Ketamine pharmacometrics

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General introduction

The phenylcyclohexylamine derivative ketamine was originally developed in the 1960s as a dissociative intravenous anesthetic agent, to replace phenylcyclohexylamine due to its severe side effects.[1] Because of the specific beneficial characteristics, such as the potent analgesic effects, the protection of the upper airway reflex and absence of clinically relevant respiratory depression, ketamine rapidly gained popularity. Interestingly, a renewed interest in ketamine has emerged in the recent years, because of new possible indications such as the treatment of treatment-resistant depression,[2] the management of different types of neuropathic pain, including chronic regional pain syndrome,[3,4] and the reversal of opioid-induced respiratory depression.[5]

However, despite the improvements in the side effect profile compared with its predecessor phenylcyclohexylamine, the wide application of ketamine is limited by serious side effects, including psychotomimetic and schizotypal effects.[1] In order to fully exploit the potential benefits of ketamine for new indications, a more thorough understanding is warranted concerning the relation between the pharmacokinetics and pharmacokinetics. However, due to the complex metabolism and the different ketamine forms currently available, the analysis of the relationship between ketamine pharmacokinetics and effects is a challenging journey.

MECHANISM OF ACTION

Historically, the N-Methyl-D-Aspartate receptor (NMDAR) was thought to be the primary receptor targeted by ketamine. Binding of ketamine to the NMDAR has been associated with its analgesic effects, but also with its dissociative anesthetic, amnesic and psychotomimetic effects.[1,6] However, more recent studies indicated that ketamine exerts its effects by binding, in addition to the NMDAR, to a wide range of receptor types including opioid receptors, sigma receptors, dopamine D_2receptors, muscarinic acetylcholine receptors, innate repair receptors and HCN1 cation channels, further adding to the complexity of ketamine pharmacodynamics.[1]

METABOLISM

Ketamine is mainly metabolized via cytochrome P450 (CYP) enzymes, of which CYP2B6 and CYP3A4 are the most important subtypes.[7,8] Although several metabolic pathways are described, the demethylation of ketamine to norketamine, with a subsequent conversion to either dehydronorketamine or hydroxynorketamine is considered to be the main metabolic pathway (Fig. 1).[9] Other, minor metabolic pathways include the hydroxylation of ketamine to hydroxyketamine and the conversion of ketamine to

hydroxyphenylketamine by CYP2C9 and flavin-containing mono-oxygenase enzymes. Furthermore, hydroxyketamine can be further converted to hydroxynorketamine.[1] Approximately 80% of the ketamine is converted to norketamine, 5% to hydroxyketamine and 15% to hydroxynorketamine.[6]

As shown in Fig 1, the cyclohexanone group of ketamine has an asymmetrical carbon, which implies that there are two types of ketamine: an *R*-enantiomer and an *S*-enantiomer. Originally, only the racemic mixture of *RS*-ketamine was marketed (Ketalar®). However, in 1997, the pure *S*-ketamine enantiomer was brought on the market as Ketanest®. Studies showed significant differences in pharmacokinetics and pharmacodynamics between those two ketamine enantiomers.[6,10-13] For example, *R*-ketamine elimination clearance has shown to be up to almost 50% lower than that of *S*-ketamine,[11-13] which might be explained by the lower affinity of CYP3A4 for *R*-ketamine compared to *S*-ketamine. Interestingly, CYP2B6 metabolizes both enantiomers with a nearly equal efficacy.[14] In addition to ketamine, stereo-selective metabolism is also likely to play a role in the formation and conversion of the metabolites.[15]

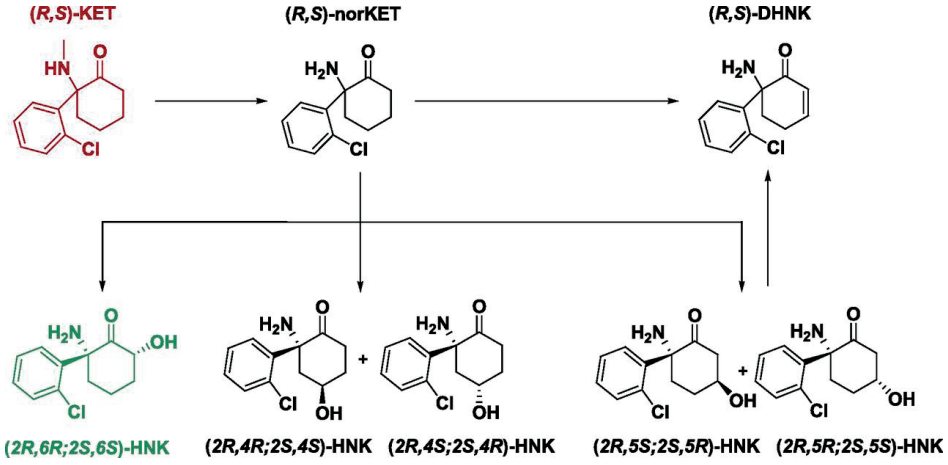

Figure 1. Main metabolic pathway of ketamine and metabolites. Ketamine (KET) is converted via CYP2B6 and CYP3A4 to norketamine. Norketamine is subsequently converted to either hydroxynorketamine (HNK) by hydroxylation or to dehydronorketamine (DHNK) by dehydrogenation. Note that norketamine can be hydroxylated at the four or the five position, resulting in different forms of hydroxynorketamine. Figure adopted from Zanos et al.[1]

THESIS OUTLINE

Although ketamine can be considered to be an "old" drug, a definitive model explaining ketamine pharmacokinetics for a wide range of patient populations, dosing regimens and ketamine administrations forms is lacking.[16] Currently, a large number of ketamine

population pharmacokinetic models is published.[17] However, the large number of ketamine pharmacokinetic models based on data from all types of study populations, ketamine dosing regimens and administration forms, can prove to become a serious challenge for clinical decision makers, since it may not always be easy to pick the model that best suits their patient population.

In this thesis, we focus on unraveling the complex pharmacokinetics and pharmacodynamics that characterize ketamine, in order to get a step closer to a final "all encompassing" pharmacokinetic-pharmacodynamic model. For the pharmacodynamic outcomes, we especially focus on the effects of ketamine on neuropathic pain, nociceptive pain (pressure pain) and psychedelic outcomes.

First, in **Chapter 2**, the role of ketamine for the treatment of neuropathic pain is studied. This chapter is an update of a previously published expert opinion, published in 2012.[18] In addition, the reader will be given some understanding of ketamine's complex metabolism.

Chapter 3 concerns a combined systematic review, meta-analysis and population pharmacokinetic modeling study that aimed to develop an overall population pharmacokinetic model for ketamine. Since a plethora of factors can influence pharmacokinetics, the effects of several important subject characteristics (weight, sex and adult *versus* pediatric, healthy *versus* patient populations) and different ketamine administration forms (*S*-ketamine, *R*-ketamine or *RS*-ketamine) are evaluated.

In **Chapter 4** the focus will remain on ketamine pharmacokinetics. However, in this chapter, stereoselective pharmacokinetic data on ketamine, norketamine, dehydronorketamine and total hydroxynorketamine obtained from randomized placebo-controlled double blind clinical study are analyzed using a nonlinear mixed effects modelling approach.

In **Chapter 5**, the cardiac output data obtained from the same study as described in Chapter 4 were analyzed by using a population pharmacodynamic modeling approach. The previously developed population pharmacokinetic model for ketamine, norketamine, dehydronorketamine and hydroxynorketamine was therefore expanded with a pharmacodynamic model to test the potential effects of each compound on cardiac output. Since potential differences in potency exist between *S*- and *R*- enantiomers for multiple pharmacodynamic outcomes,[19-22] we included an evaluation of the separate effects of *S*- and *R*-enantiomers on the cardiac output.

Finally, in **Chapter 6**, we aimed to develop a population pharmacodynamic model to describe the effects of *RS*-ketamine and *RS*-norketamine on the pressure pain threshold and psychedelic symptoms, defined as external perception.

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2

Pharmacokinetic and pharmacodynamic considerations for NMDA-receptor antagonist ketamine in the treatment of chronic neuropathic pain: an update of the most recent literature.

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NEUROPATHIC PAIN

On their website, the International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as "pain caused by a lesion of the somatosensory nervous system".[1,2] The IASP further states that NP is a description rather than a diagnosis that requires a detectable lesion or a disease according to recognized neurologic criteria. NP may be central or peripheral depending on the location of the lesion in the peripheral or central somatosensory nervous system. It is evident from these statements that NP is associated with multiple diseases or syndromes (Table 1).[3] Additionally, in many patients no cause for their NP is found.

Table 1. Examples of diseases and syndromes associated with neuropathic pain.

Trauma to the peripheral or central nervous system	Surgical trauma, spinal cord injury, traumatic peripheral nerve damage, amputation with phantom limb pain, complex regional pain syndrome, complex regional pain syndrome
Nerve or spinal cord compression	Disc herniation, canal stenosis
Vascular disease	Stroke, ischemia of the lower extremities
Degenerative neurological disease	Multiple sclerosis, amyotrophic lateral sclerosis, syringomyelia, Parkinson's disease, Huntington's disease, Alzheimer's disease
Infectious disease	HIV/AIDS, leprosy, shingles, neuritis
Hereditary neuropathic syndromes	Erythromelalgia, Fabry's disease, sodium channelopathy
Metabolic syndromes	Diabetes mellitus, sarcoidosis, alcoholism, amyloidosis, malnutrition, obesity
Drugs and toxins	Chemotherapeutics, thalidomide, arsenic
Cancer	Paraneoplastic, dysglobulinemia, nerve damage (in cancer pain often both neuropathic and nociceptive components are present)
Other	Idiopathic, fibromyalgia

Patients with NP often display similar characteristic symptoms irrespective of the underlying disease, such as spontaneous pain often described as burning (hot), electric or shooting, an increase in pain sensitivity (hyperalgesia) with reduced pain thresholds (allodynia).[3] In case of hyperalgesia and allodynia there is often central sensitization or a heightened responsiveness of nociceptive neurons to normal and subthreshold inputs.[4] The presence of central sensitization can be examined by so called experimental proxies such as conditioned pain modulation or temporal summation in humans and windup in animals.[4] It is important to realize that, particularly in case of central sensitization, there is a discrepancy between the amount of tissue damage and the intensity of pain experienced by the patient, due to the fact that aberrant pain processing within the central nervous system is now the main cause of the pain.[4]

Many chronic pain syndromes, including and possibly even especially NP, are associated with comorbidities such as depression, anxiety, difficulty sleeping, fatigue, cognitive decline, and other often poorly diagnosed vague symptoms such as diffuse bodily pain or general malaise.[5] In conclusion, NP is a debilitating condition associated with an often difficult-to-treat underlying (or idiopathic) disease that has a major impact on the well-being of the patient and may have serious socioeconomic consequences to the affected individual and his or her family.

TREATMENT OF NEUROPATHIC PAIN

NP is difficult to manage with just a limited treatment effect in 30-60% of patients. Most, if not all, treatments are aimed at symptom reduction. In 2015, Finnerup et al. published a systematic review and meta-analysis of randomized controlled trials of oral and topical pharmacotherapy *versus* placebo to treat NP.[6] They used the number-needed-to-treat (NNT) as primary end-point, where an effective treatment was defined by a reduction in pain score by at least 50%. There was no evidence of efficacy for any drug in in any disease. Hence, irrespective of underlying disease, they observed an average NNT of 3.6 for tricyclic antidepressants and number-needed-to-harm (NNH) of 13.4; NNT of 6.4 for SNRI-(selective serotonin-noradrenaline reuptake inhibitors; mainly duloxetine)-type antidepressants (NNH = 11.8); 7.2 for gabapentin (NNH = 29) and 7.7 for pregabalin (NNH 13.9), both anticonvulsants. NNT and NNH values for strong and weak (tramadol) opioids were 4.3 and 4.7, respectively, with NNH values of 11.7 and 12.6. Based on the quality of evidence and efficacy, the authors give a strong recommendation for use of antidepressants (tricyclics and SNRIs) and GABAergic anticonvulsants, and a weak recommendation for use of opioids and the lidocaine (5%) and capsaicin (8%) patches. The recommendation regarding the use of oral or topical N-methyl-D-aspartate receptor (NMDAR) antagonists was inconclusive. Finnerup et al. did not include intravenous NMDAR antagonists, such as ketamine, in their analyses.[6]

Since the NMDAR plays a crucial role in the development and chronification of pain, especially NP, and given the fact that the current array of treatment options still lacks adequate efficacy in the majority of patients, many physicians in second and third line attempt treatment of refractory NP with NMDAR antagonists, particularly ketamine.[7-9] In chronic NP, there is an enhanced release of the excitatory amino acids (glutamate) in the dorsal spinal horn of the spinal cord, with consequently persistent activation of post-synaptic excitatory NMDARs that maintain afferent neurotransmission to sensory brain sites.[7] Prolonged stimulation will cause upregulation of the NMDAR and consequently establishes a state of central sensitization with pain, allodynia and hyperalgesia, often spreading across multiple dermatomes. Note that sensitization is not restricted to NP but

may also occur in nociceptive pain.[4] Given the above, blockade of sensitized NMDARs seems an opportunistic method of pain relief in NP by curtailing central sensitization. There are several drugs available in clinical practice with (variable) antagonistic activity at the NMDAR including xenon, nitrous oxide, magnesium, methadone, amantadine, riluzole, memantine, phenytoin, carbamazepine, valproic acid and ketamine.[10,11] Just a restricted number of these drugs are used to specifically treat NP. The largest number of positive trials in the treatment of NP is observed with ketamine.[11] Of all mentioned NMDAR antagonists, ketamine is possibly most efficacious in reducing windup and temporal summation.[12] In a recent study in patients with refractory NP, temporal summation measured just before treatment was a predictor of the efficacy of ketamine. [13]

In this review, we discuss recent data on the pharmacokinetics and pharmacodynamics of ketamine in the treatment of NP. This is an update of our previous review on this same topic published in 2012.[7] Since then, the interest in ketamine and other NMDAR antagonists has increased significantly, primarily due to the positive results of studies on the treatment of therapy-resistant depression with ketamine. Moreover, the use of ketamine in the management of several refractory (neuropathic) pain conditions persists. Alongside the increased clinical interest in ketamine, new data have emerged on the pharmacokinetics of ketamine and its metabolites, and on the complex and comprehensive modes of action of ketamine in its intended and adverse effects. Finally, additional studies were published that scrutinized ketamine efficacy, particularly in NP conditions.

KETAMINE

Ketamine is a rather complex drug; it is a racemic mixture containing an *S*- and *R*-isomer.[7,8] Since 2000, both the racemic mixture (Ketalar® or *RS*-ketamine) and the *S*-ketamine enantiomer (Ketanest®, Spravato® or esketamine) are commercially available. Additionally, ketamine has several active metabolites. Major metabolites include norketamine (NK) and hydroxynorketamine (HNK), of which multiple enantiomers are produced in the liver.[14] (2*R*,6*R*)-HNK is the most studied ketamine metabolite due to its specific pharmacodynamic properties. Both enantiomers and metabolites differ in their pharmacokinetics and pharmacodynamics (such as molecular site of action), although detailed information on these differences is still not fully available.[14] Therapeutically, ketamine is used as anesthetic, analgesic for acute and chronic (cancer and non-cancer) pain, and since a few years as antidepressant. Additionally, ketamine is occasionally used as anti-inflammatory agent in perioperative care, in the treatment of post-traumatic stress disorder, and finally to induce bronchodilation in refractory asthma. [15-17]

MECHANISM OF ACTION

Ketamine is a promiscuous drug that interacts with multiple receptor systems within the central nervous system (*e.g.* opioid receptors, sigma receptor, dopamine D_2 receptors, muscarinic acetylcholine receptor, innate repair receptor, HCN1 cation channels).[7,8] In NP, however, its main mechanism of action is blockade of sensitized NMDARs.[7,8] As discussed previously, this will interrupt the continuing and excessive barrage of afferent input from damaged peripheral sites (such as a peripheral nerve injured by surgery).[7] Secondary mechanisms include the reset or desensitization of spinal and supra-spinal glutamatergic nociceptive pathways, the inhibition of reuptake of monoaminergic compounds (*e.g.* dopamine, serotonin and norepinephrine) and the restoration of descending pain inhibition.[8] An interesting recent observation is that ketamine does not produce relief of NP in mice lacking the β-common receptor (CD131).[18] The erythropoietin receptor-β-common receptor complex (also named the innate repair receptor) is a tissue protective receptor that is upregulated in tissue injury (including various diseases associated with NP) and activated by the local release of erythropoietin. Ketamine acts at the innate repair receptor causing effective relief of allodynia in wild type mice and rats. NP persists in knockout mice that lack the β-common receptor. Interestingly, acute pain relief was still observed in these β-common receptor knockout mice. It was argued that ketamine acts *via* a yet unknown link between the NMDAR and this specific repair pathway. An interesting secondary observation was that ketamine reduced inflammatory markers in the spinal cord of rats with NP from peripheral nerve damage.

PHARMACOKINETICS

Ketamine inhalation

Ketamine is administered by several routes of administration including intranasal, sublingual, subcutaneous, rectal, transcutaneous and intravenous routes. However, in clinical practice, the intravenous route is the most frequently applied mode of ketamine delivery with consequently the need for a venipuncture or intravenous cannula. Recent studies addressed the safety and feasibility of ketamine inhalation following nebulization or aerosolization of preservative free *RS*- and *S*-ketamine.[19,20] The main rationale for this route is the ability to administer ketamine for longer periods of time without the need for intravenous access. Additionally, inhalation results in a rapid absorption into the systemic circulation, which is only surpassed by intravenous administration. Inhaled ketamine could be an alternative mode of delivery outside of the hospital setting (for example at home in palliative care).

The safety of preservative free *S*-ketamine inhalation was addressed by Jonkman et al.[20] They showed rapid *S*-ketamine uptake with C_{MAX} values > 100 ng/mL attained within 15-30 min, following inhalation of 0.35-0.70 mg/kg *S*-ketamine for 20-40 min. All adverse effects that were observed were related to the drug itself and not to the mode of administration and were perceived as mild. Side effects included nausea, vomiting, drug high, schizotypal effects and mild hypertension. None of these side effects interfered with the operation of the inhalation device. During and following inhalation, there were no signs of oropharyngeal irritation, hypersalivation, stridor, laryngospasm, bronchospasm, dyspnea, aspiration or desaturation.

In a second publication, Jonkman et al. addressed the pharmacokinetics and bioavailability of inhaled ketamine.[19] The pharmacokinetic data were analyzed with a multicompartmental model that consisted of three *S*-ketamine, two *S*-norketamine disposition and three metabolism compartments. Uptake into the systemic circulation was modelled through a rapid (immediate) and a slow pathway with rate constant 0.05 min^{-1}, probably related to pulmonary uptake. Bioavailability ranged from 40 to 70%. Thirty percent of the *S*-ketamine was lost due a dose-independent mechanism (ketamine swallowed, exhaled or stuck to the inhalation device) while the remainder was lost in a dose-dependent fashion, probably due inefficient inhalation. No safety issues became apparent in bystanders (research personnel).

Intranasal ketamine

Similar to ketamine inhalation, the delivery of ketamine via a nasal spray is possible without intravenous access, and thus facilitates ketamine use in outpatient settings. In a study by Nielsen et al., fifty children received a combination of intranasal sufentanil (0.5 µg/kg) and racemic ketamine (0.5 mg/kg) preceding painful procedures.[21] Ketamine bioavailability was 36%, with C_{MAX} values > 100 ng/mL reached after 8.5 min. The authors reported few adverse effects (vomiting in three patients). Recently, the FDA approved an intranasal *S*-ketamine preparation (Spravato®; Johnson & Johnson) for management of treatment-resistant depression (*i.e.,* for patients who experienced previous treatment failure with two other antidepressants without success).[22] Spravato® should be used in conjunction with an oral antidepressant. The intranasal device delivers 28 mg of *S*-ketamine in two sprays and is available as a 56-mg kit (two 28-mg devices) or an 84-mg kit (three devices). Dosing is 56 or 84 mg once weekly but eventually (after 8 weeks) aimed at an individualized dosing frequency to the least frequent dose that maintains remission or treatment response.

Ketamine pharmacokinetic model parameters

We recently performed a meta-regression analysis to synthesize ketamine PK parameter values, volume of distribution and terminal clearance, and determined a possible

effect of age, disease state, administration form (*S*- or *RS*-ketamine), analyte (*S*-, *R*- or *RS*-ketamine), sampling site (arterial or venous) and population size.[23] Data from 30 ketamine PK modeling studies were retrieved from the literature. Interestingly, despite sometimes large inter-study heterogeneities, the values for volume of distribution and elimination clearance were similar among studies with values for volume of distribution 200-270 L/70 kg (95% confidence interval) and for elimination clearance 70-85 L/h at 70 kg. Additionally, no influence of any of the covariates on PK parameters was observed. This indicates that one set of ketamine model parameters may be used to determine dosing in a variety of conditions. However, dosing in the pediatric population remains preferable by titration to effect rather than dosing by body weight as these analyses were scaled to a standardized 70 kg patient. Due to a paucity of studies, assessment of the effect of metabolic enzyme variants or sex on model parameters was not possible. Similarly, just a minority of studies included ketamine's metabolites into their PK models and hence it remains unclear whether inclusion of these metabolites would improve the performance of ketamine PK (and PD) models.

Metabolites

Ketamine is extensively metabolized via cytochrome P450 (CYP) enzymes, mainly by CYP2B6 and CYP3A4. The main metabolic pathway involved in ketamine metabolism is N-demethylation to NK. Subsequently, NK can be either hydroxylated to HNK or dehydroxylated to dehydronorketamine (DHNK). In addition, several minor metabolic pathways have been described, most of them involving the conversion of ketamine to hydroxyketamine with or without a subsequent conversion to HNK.[24] Approximately 80% of the ketamine dose is metabolized to NK, 5% to hydroxyketamine and 15% to HNK. [25-27] The relative importance of CYP enzymes 2B6 and 3A4 in the metabolic pathways of ketamine remains a matter of debate. A recent *in vitro* study showed a higher ketamine affinity for CYP2B6 than CYP3A4 for ketamine N-demethylation to NK in human liver microsomes.[25] However, since CYP3A4 is more abundant than CYP2B6, CYP3A4 is considered to be the main CYP subtype in this metabolic pathway. Ashraf et al. report that CYP2B6 is the main enzyme responsible for ketamine metabolism.[28]

It is well known that CYP polymorphisms can substantially influence ketamine clearance and thus plasma concentrations. In a study evaluating the effects of CYP2B6 polymorphisms and age on ketamine clearance, the presence of the CYP2B6*6 allele explained 40% of the variation in ketamine steady state concentrations.[29]

One recent study in patients with treatment resistant bipolar disorder allowed extraction of relevant PK parameter values for HNK and DHNK.[30] Assuming that central volumes of distribution for HNK and DHNK are equal to that of ketamine, clearances were 4.7 L/h at 70 kg, 15.2 L/h at 70 kg and 8.34 L/h at 70 kg for HNK, *R*-DHNK and *S*-DHNK. Total plasma exposure (area under the curve, AUC) was shown to be higher for

the HNK metabolite than for ketamine, which is likely to be caused by rapid and efficient metabolic generation of HNK combined with a relatively slow HNK clearance.

Enantiomers

In agreement with earlier observations, Henthorn et al. report a 15% lower *R*- than *S*-ketamine clearance following the separate administration of the two ketamine enantiomers in healthy volunteers.[31] A part of the stereoselective metabolism may be explained by the higher affinity of CYP3A4 for *S*- than *R*-ketamine, which results in a higher metabolic rate for *S*-ketamine. In contrast, demethylation by CYP2B6 occurs with near similar efficiency for both enantiomers.[24] Rat studies indicate the importance stereoselective metabolism of ketamine into HNK.[32] Moaddel et al. showed that the *S*-ketamine enantiomer is a more efficient source of (2,6)-HNK than the *R*-enantiomer.[32] However, HNK brain uptake and the clearance from plasma were not enantioselective. These results point towards similar enantioselectivity in the metabolism of ketamine into NK and HNK in humans and rats.

PHARMACODYNAMICS

Systematic reviews and randomized trials

A large number of studies on the efficacy of ketamine in pain management has been conducted and numerous clinical trials and case series have been published since 1990. In 2012 we stated that with respect to the ability of NMDAR antagonists in general and ketamine in particular to relief neuropathic pain "... *good-quality RCTs are sparse and point to just one NMDAR antagonist, ketamine, as a possible tool in the treatment of neuropathic pain. Still also for ketamine the proof is limited* ....".[7] To determine whether this picture on ketamine persists, we searched for systematic reviews published since 2012 that evaluated randomized controlled trials on the efficacy of ketamine (irrespective of administration route) in chronic pain conditions with a neuropathic pain component. We also included cancer pain, since cancer pain is often a mixed form of nociceptive and neuropathic pain. We retrieved seven relevant meta-analyses, systematic or literature reviews (Table 2). Five reviews focus on chronic neuropathic pain,[11,33-36] of which two predominantly on complex regional pain syndrome (CRPS) patients,[35,36] and two reviews on cancer pain.[37,38] Although there is some overlap in studies included in the various reviews, the approach of the different reviews is sufficiently distinguishing to be included in our analysis. The overall picture that emerges from these reviews is that (1) the heterogeneity among studies is large and synthesis of data is often not possible; (2) irrespective of the underlying disease, intravenous administration of ketamine seems to have a higher efficacy than other administration forms (oral, subcutaneous,

intranasal or topical); (3) the efficacy of intravenous ketamine is often rather small and does not last longer than 1-2 days following end of administration; (4) longer infusion times are associated with longer effect durations; (5) none of the studies phenotyped their patients or restricted treatment to patients with central sensitization; and (6) most studies were effectively not blinded due to the occurrence of ketamine side effects. One randomized controlled trial on the effect of oral ketamine *versus* placebo in cancer-related neuropathic pain was not included in any of the reviews and deserves mentioning. Fallon et al. randomized 214 patients with chemotherapy-induced neuropathic pain.[39] A ketamine or placebo titration phase was followed by a pain control maintenance phase. Just 24 and 26 patients in the respective ketamine and placebo arms completed the study. The others were excluded in the titration or maintenance phase due to treatment failure. Overall, ketamine was equivalent to placebo with 31.8% (ketamine) and 36.4% (placebo) of patients displayed maintained analgesic benefit at day 4 of treatment and 22.4% (ketamine) and 25.2% (placebo) at day 16. The authors further mention that there still may be subgroups of patients, such as those with central sensitization, that may be sensitive to the analgesic effects of ketamine. However, they did not phenotype patients in their study.

Finally, one important therapeutic indication for ketamine is its ability to provide long-term pain relief in opioid-dependent chronic low-back pain patients following low-back surgery.[40,41] The pathology causing low-back pain and the trauma from surgery will have neuropathic pain components and ketamine might have beneficial effects in subduing central sensitization and chronification. Additionally, the long-term use of opioids may have worsened central sensitization and consequently may have amplified hyperalgesia and allodynia. A recent randomized placebo-controlled trial studied patients undergoing spinal fusion surgery for chronic low-back pain.[41] Patients who had moderate to severe low-back pain (average pain score 50 mm, on a 0 to 100 mm scale) for at least 3 months and consumed an opioid for at least 6 weeks, were treated with either ketamine or placebo (bolus 0.5 mg/kg, followed by an infusion of 0.25 mg/kg per h) during the surgical procedure. Compared to placebo, ketamine-treated patients that preoperatively consumed more than 0.5 mg/kg intravenous morphine equivalents per day, used less morphine in the first 24 and 48 h following surgery; patients using less daily morphine equivalents preoperatively did not benefit from morphine in the first 24 and 48 postoperative hours. Most importantly and irrespective of prior opioid dose, patients treated with ketamine displayed significantly more improvement of their back pain after 6 months compared to placebo-treated patients and had less disability. At that time 44% of patients in the ketamine group and 62% of patients in the placebo group still had a daily consumption of opioids. Moreover, after 1 year these patients had less pain at rest and during mobilization (mean difference 13-17 mm) and used fewer opioid analgesics (ketamine group 0-20 mg/day *versus* placebo 0-62 mg/day, $p = 0.02$).[42]

Table 2. Meta-analyses, systematic and literature reviews on the efficacy of ketamine in the treatment of chronic (neuropathic) pain.

Authors/ type of analysis	Disease	Number of RCTs included	Number of patients	Ketamine efficacy	Comments
Orhurhu et al. 2019/ meta-analysis [34]	Chronic (neuropathic) pain	7	211	Small positive effect of intravenous ketamine.	Effect lasting for 2 weeks after ketamine infusion with a pain reduction of 1.83 points with 95% ci -2.35 to -1.31.
Aiyer et al. 2018/ literature review [11]	Chronic neuropathic pain	21	548	15/21 trials showed some (non-specified) benefit, of which 13/13 i.v. ketamine studies showed some benefit.	Oral (n = 3), topical (n = 5) and intravenous ketamine studies (n = 13) were included.
Zhao et al. 2018/ meta-analysis [36]	Complex Regional Pain Syndrome	15	258	A small meaningful reduction in pain scores was observed immediately following treatment and after 1-3 months.	The number of patients with at least 30% pain relief was 69% with 95% ci 53 to 84%, immediately after treatment and 58% (41 to 75%) 1-3 months after treatment.
Michelet et al. 2017/ meta-analysis [33]	Chronic neuropathic pain	6	195	No effect at 4 weeks after the beginning of ketamine treatment was observed although analyzing just the studies with no high-risk bias did find a moderate effect.	Leaving the one study with high-risk bias out of the analysis leads to a pain reduction of -1.73 points with 95% ci -2.39 to -1.07.
Bell et al. 2017/ systematic review [37]	Cancer pain	3	215	Two small studies (total n = 30) reported small reductions in pain intensity and morphine requirements. The larger trial (n = 185) showed no difference in pain scores between subcutaneous ketamine and placebo.	Various administration routes: intravenous, intrathecal and subcutaneous.
Jonkman et al. 2017/ literature review [38]	Cancer pain	4	245	3 of 4 trials had a negative effect; the remaining trial had an effect lasting no longer than 3 hours following the end of treatment.	Two additional trials are discussed on epidural (n = 12) or intrathecal (n = 20) ketamine + morphine *vs.* just morphine. Pain scores did not differ between treatments.
Connolly et al. 2015/ literature review [35]	Complex Regional Pain Syndrome, breakthrough pain, and postherpetic neuralgia	5	107	4 of 5 trials with intravenous (n = 3) and intranasal (n = 1) ketamine showed some efficacy; topical ketamine was without effect in Complex Regional Pain Syndrome patients.	

These reports contrast outcome of several other trials that show just limited effects of ketamine treatment during a range of surgeries for prevention of persistent postoperative pain.[9] However, none of the included patients in these earlier trials were opioid-dependent. It may well be that in opioid-dependent patients, ketamine interacts with brain circuits involved in opioid rewarding, causing a neuronal reset and consequently fewer opioid requirements (without withdrawal symptoms), re-engagement of descending pain inhibition and reversal of opioid-related paradoxical effects (opioid-induced hyperalgesia). A recent case report confirms such mechanisms.[43] A patient with CRPS and severe pain (score 9 out of 10) consuming daily more than 300 mg of morphine equivalents was successfully and rapidly opioid tapered with two 5-day ketamine treatments and cognitive behavioral therapy and remained opioid free for up to 1 year.

(2*R*,6*R*)-hydroxynorketamine

While it is generally accepted that ketamine is most important in producing the analgesic effects, it may well be that, in parallel to ketamine treatment in depression, the active metabolites play an important role in ketamine analgesia. In three mouse models of pain (nerve-injury neuropathic pain, tibia fracture complex regional pain syndrome pain, and plantar incision postoperative pain), Kroin et al. compared the analgesic effects of (2*R*,6*R*)-HNK and ketamine.[44] In all three models, (2*R*,6*R*)-HNK was superior to ketamine in producing long-lasting (> 24 h) relief of allodynia. Since the half-life of (2*R*,6*R*)-HNK is less than 1-h in the mouse brain, these effects are not pharmacokinetically driven but are possibly related to neuroplastic and neurotrophic changes causing reduction of central sensitization. Importantly, unlike ketamine, (2*R*,6*R*)-HNK is not associated with motor incoordination and has a lower potential for abuse or addiction. Further, this metabolite is associated with profound antidepressant effects. These observations make (2*R*,6*R*)-HNK an attractive new candidate analgesic. Zanos et al. showed that (2*R*,6*R*)-HNK antidepressant actions are independent of the NMDAR but are related to agonistic activity at the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor.[14] Whether a similar mechanism plays a role in the analgesic effects of (2*R*,6*R*)-HNK is still unknown.

ADVERSE EFFECTS

In humans, ketamine produces undesirable adverse effects that limit treatment compliance. Similar observations are made in animal studies. For example, in rodents, ketamine causes hyperlocomotion, ataxia and stereotypical behavior such as continuous running, head weaving, shaking or twitching.[45] In humans, symptoms include drug high, dissociative or psychedelic effects with psychosis-like behavior (paranoia,

hallucinations, changes in internal and external perception) and severe anxiety with panic attacks.[46] Treatment is aimed at symptom reduction with benzodiazepines and α_2-adrenergic receptor agonists (*e.g.* clonidine). One possible explanation for the occurrence of psychedelic effects during ketamine exposure is related to hypofunction of the NMDAR.[47-50] Upon glutamatergic NMDAR activation, calcium-ions flow into the cell and bind to calmodulin that stimulates nitric oxide (NO) synthase to produce the gaseous neuromodulator NO from L-arginine. Nitric oxide subsequently activates a cascade that in the end has neuroplastic, neurotrophic and neuroprotective effects. Blockade of the NMDAR by ketamine reduces the intracellular NO production causing the loss neuronal stability with consequently generation of negative behavioral symptoms. In animals, increasing intracellular NO content using NO donors blocks both phencyclidine and ketamine behavioral responses, attenuates ketamine-induced memory deficits, and reduces social withdrawal and anxiety.[47-51] Interestingly, there are data that show improvement of schizophrenia symptoms with the NO donor sodium nitroprusside (SNP).[51]

In one recent experimental study performed in healthy volunteers, the influence of the NO donor SNP was studied on drug high and changes in internal and external perception during infusion of racemic ketamine and *S*-ketamine.[52] Relative to placebo, SNP significantly reduced symptoms during and following racemic ketamine but not during and following *S*-ketamine infusion, suggesting that the symptoms induced by R-ketamine are alleviated by NO. Since the affinity of *S*-ketamine for the NMDAR is fourfold higher than that of *R*-ketamine, possibly higher SNP doses (causing more NO release) may be required to counteract *S*-ketamine-induced symptoms. However, it may equally be that the two ketamine isomers activate divergent intracellular transduction pathways, one of which is NO sensitive and the other is not. At present, adding a NO donor during racemic ketamine treatment for chronic pain seems premature and unsubstantiated. Possibly part of ketamine's intended effect is mediated by its dissociative pathway. For example, in the treatment of depression with ketamine, dissociative effects may play a modulatory role.[53] Hence, further (animal) studies are needed to assess whether modulation of the NMDAR-calmodulin-NO pathway negatively affects engagement of antidepressant and analgesic pathways.

CONCLUSIONS

The interest in ketamine has increased over the last decade. This is predominantly related to the development of ketamine for treatment of patients with therapy-resistant depression. This resulted recently in the approval by the FDA of the intranasal *S*-ketamine application Spravato® for this treatment indication.[22] The consequence of these developments is that knowledge on ketamine metabolomics has increased

significantly. While an important role for hydroxynorketamine has been detected in treatment of depression, just one experimental study studied the anti-allodynic effects of this ketamine metabolite in neuropathic and postoperative pain.[44] The results are promising, not only because of long-lasting analgesic efficacy, but also because this specific metabolite has fewer side effects than ketamine. Interestingly, the long-lasting analgesic effect is not driven by HNK pharmacokinetics. It is therefore likely that the metabolite has neuroplastic and/or neurotrophic effects at spinal and supraspinal sites that effectively counteracts central sensitization. Similar modes of action have been proposed for ketamine and are thought to be related to prolonged NMDAR desensitization.[54,55] Further studies are needed to fully understand the mechanism of action of HNK in pain relief. In the meantime, we encourage further development of HNK in humans for the treatment of pain.

Akin the recent development of esketamine intranasal application, inhalation as route of administration opens the possibility of long-term ketamine treatment outside the conventional hospital setting, for example in palliative care at home or in a hospice.[19,20] Since long-term treatment rather than short high-dose infusions seems to be crucial in effective management of chronic NP, this application form has an evident advantage over the intranasal form. The inhalation of esketamine is safe, but a practical inhaler has not been developed yet.

The following conclusions may be drawn from the seven systematic reviews and meta-analyses that were published since 2012[11,33-38] : irrespective of underlying disease, intravenous administration of ketamine seems to have the highest analgesic efficacy compared to other administration forms; the efficacy of intravenous ketamine is often rather small and does not last longer than 1-2 days following end of administration; longer administration times are associated with longer effect durations; none of the studies phenotyped their patients or restricted treatment to patients with central sensitization; most studies were effectively not blinded due to the occurrence of ketamine adverse effects.

EXPERT OPINION

The most important conclusion from the current update is that our current findings on the efficacy of ketamine to treat chronic neuropathic pain are in agreements with our conclusions from 2012 that *definitive proof of the efficacy of ketamine in management of neuropathic pain is limited*, with just small analgesic effects lasting no longer than a few days or (in some studies employing long-term infusion paradigms) a few weeks.[7] In 2012, we stated that additional randomized studies were urgently needed. We currently doubt whether additional randomized trials in often ill-defined groups of chronic

pain patient groups are useful and suggest to restrict future studies to patients with neuropathic pain and signs of central sensitization or to patients with opioid refractory severe neuropathic pain.

It is important to realize that the results of these systematic reviews on randomized controlled trials sharply contrast the findings from observational studies and case series. As discussed earlier, most open studies show unequivocally that ketamine has benefit in the management of chronic pain with positive patient-related outcome measures.[7,55] Additionally, experimental human and animal studies show analgesic efficacy of ketamine in neuropathic pain. We recently gave several explanations for the gap between controlled trials and open-label or case studies. In short, randomized controlled ketamine trials may fail for the following reasons[9,38] :

(1) Short-term infusions of ketamine will cause effects no longer than the treatment period or for just hours to a few days after treatment. Most trials on long-term intravenous treatment show greater signals of efficacy lasting days to weeks;
(2) Often the ketamine dose is restricted because of fear of adverse effects. Co-administration of benzodiazepines and/or α_2-agonists may be helpful. Especially, α_2-agonists may be useful as they are analgesic by themselves and temper the hemodynamic effects of ketamine;
(3) Rigid dosing titration regimens will have a negative effect on personal analgesic needs of the patient. In real life rapid and loose up-and-down titrations are allowed, aiming at optimizing effect with as few as possible side effects and often combined with co-medication;
(4) Pain intensity scores are often not well understood by patients and additionally may not capture the beneficial effects of ketamine on mood, cognition and quality of life. Linear metric scores on a 100 mm scale or numerical ratings poorly represent the actual perceived pain, particularly under conditions of chronic pain and cognitive impairment[56,57]. Moreover, ketamine may affect cognition and consequently more qualitative than quantitative scoring systems are likely required;
(5) Placebo controls may cause a bias in study outcome either due to an inflated placebo effect or due to the fact that well-informed clinical-trial participants that experience absence of side effects may decide to terminate their participation in the study[58]; and finally,
(6) In real life, patients with severe and progressive neuropathic pain often have other symptoms or complaints that restrict their ability to be included in the trial.

The debate on the efficacy of ketamine in the treatment of chronic neuropathic pain is certainly not closed. But more inventive ketamine studies than rigid randomized controlled trials are required before we can come to definite conclusions.[59] Possibly, restricting treatment to patients with specific neuropathic phenotypes and/or using

standard practice as control may result in a synthesis of randomized and open trials. Trials in which patients with central sensitization, irrespective of the cause of the underlying NP syndrome, *versus* those without central sensitization are needed to assess whether this subpopulation of patients is best served with long-term ketamine treatment. Other subpopulations that may benefit from ketamine are those chronic pain patients with confirmed small fiber neuropathy, larger nerve damage, central pain or patients with opioid-induced hyperalgesia. In other words, future ketamine trials should include patients with specific NP manifestations rather than patients suffering from general NP with a certain level of pain intensity. Additionally, apart from pain-related biomarkers, other study endpoints are needed. For example, mood-related indices and other patient-related outcome measures related to quality-of-life, daily activity and sleep quality/duration may better reflect the effect of ketamine on the patient's overall condition.

Finally, the use of ketamine for chronic NP should be viewed in light of the current opioid epidemic. Opioids are currently prescribed for a myriad of pain conditions including NP. The surge in opioid consumption has devastating consequences of which addiction, abuse and often fatal respiratory depression are common.[60,61] Two questions come to mind: (1) is ketamine a viable replacement of opioids for treatment of NP? and (2) is the treatment of ketamine safe when administered in combination with opioid therapy? The response to the first question is that ketamine should be used exclusively in therapy-resistant NP with clear signs of central sensitization or in opioid-tolerant patients. Treatment should always be offered under the supervision of health care providers in a healthcare setting. Additionally, one needs to realize that ketamine produces a drug high and, in high dose, a dissociative state. It can be addictive and may be abused (worldwide, ketamine is a popular party drug). Ketamine abuse is associated with a variety of adverse effects including liver failure and hemorrhagic cystitis.[8,62] These factors should be considered when considering ketamine treatment. The second question has recently been addressed by Jonkman et al. They showed that ketamine effectively counteracts opioid-induced respiratory depression, possibly through its (indirect) actions at the AMPA receptor.[63,64] This is an important observation that is relevant in perioperative care as well in NP patients treated with (high dose) opioids.

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3

Ketamine pharmacokinetics: a systematic review of the literature, meta-analysis and population analysis

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The *N*-methyl-D-aspartate antagonist ketamine, a derivative of phenylcyclohexylamine, was introduced as intravenous anesthetic agent in the 1960s as replacement of phencyclidine.[1] Ketamine gained rapid popularity due to its specific properties such as protection of the upper airway reflex, lack of significant respiratory depression and potent analgesia. Recently, renewed interest in ketamine emerged, because of potentially new indications, such as management of chronic pain, treatment of therapy-resistant depression and reversal of opioid-induced respiratory depression.[1-3] However, ketamine is a complex drug since it has two isomers (*R*- and *S*-enantiomers) and multiple (active) metabolites. Furthermore, ketamine has some serious psychotomimetic or schizotypal adverse effects that reduce treatment compliance. There are two administration forms: the racemic mixture (Ketalar) and the *S*-enantiomer (intravenous Ketanest and intranasal Spravato).

Data describing the relation between ketamine dosing and its subsequent plasma concentrations can greatly aid in the development of dosing schemes that are intended to maximize therapeutic effects while limiting side effects, by reducing over- and under-dosing. Population pharmacokinetic modelling is a method that mathematically describes the relation between dose and plasma concentration.[4] Mixed-effect models are mathematical models that not only include structural model elements, such as drug clearance or volume of distribution, but also incorporate random effects, *e.g.* variability of these parameters within a study population. By considering random effects in a model, a more accurate description of the data can be obtained.

A broad range of ketamine pharmacokinetic models, differing in both structure and complexity, has been published to describe ketamine pharmacokinetics in different populations and after different methods of administration or blood sampling. In the current study, we performed a systematic review of relevant studies, to qualitatively and quantitatively evaluate existing pharmacokinetic models of ketamine and its metabolite, norketamine. We did not include other metabolites since no model data are currently available. We developed a quality scoring system to get an indication of the quality of the modeling analyses and the presentation of the modeling results. Next, we performed three analyses to get a general indication of ketamine pharmacokinetics: (1) we performed a meta-analysis to get the mean weighted parameter estimates and assessed the influence of specific covariates (health status, age (adult *versus* pediatric), formulation, sampling site (arterial *versus* venous), analyte (*S*- or *R*-enantiomer, racemic ketamine) and population size); (2) we constructed a meta-analytical three-compartment ketamine pharmacokinetic model from studies that analyzed the ketamine data with a three-compartment model; (3) and finally, we developed a pharmacokinetic model by analyzing raw data sets, and compared the output of the model with the data derived from the meta-analysis. The primary aim of our study is to qualitatively and quantitatively evaluate existing ketamine pharmacokinetic models and construct a ketamine pharmacokinetic meta-analytical model.

MATERIALS AND METHODS

The meta-analysis was performed according to the PRISMA guidelines.[5,6] The study protocol was prospectively registered on the PROSPERO website (crd.york.ac.uk/prospero; registration number CRD42018107633). Only observational and experimental studies reporting pharmacokinetic model analyses of ketamine (racemic, *S*- or *R*-ketamine) with or without ketamine metabolites were included. Furthermore, only human (adult or pediatric) studies reporting on intravenously administered ketamine (racemic, *S*- or *R*-ketamine) were included; records reporting animal, *in vitro* studies, reviews, conference abstracts or editorials were excluded.

Record search strategy and selection

Pubmed, EMBASE and Web of Science databases were systematically searched for relevant literature on September 5, 2018. Search terms included ketamine, esketamine, pharmacokinetics, (theoretical) models and specific pharmacokinetic terms (including absorption, area-under-the-curve, bioavailability, biotransformation, metabolism, clearance, elimination, distribution, excretion, half-life, disposition). A complete overview of the search strategies may be obtained from the authors. The obtained records were searched for duplicate papers that were removed. To come to a final selection, eligible full texts were independently evaluated by two reviewers (JK, EO). Inclusion criteria were (1) original data; (2) intravenous ketamine administration; (3) a human study population; (4) the presence of a population PK analysis of the ketamine PK data; (5) if criteria 1-4 were present, sufficient data should be presented to allow for parameter recalculation (see below). Furthermore, the references of all selected papers were screened for additional relevant studies not detected in the initial literature searches.

Quality assessment

There are several validated assessment tools available that assess the quality of randomized controlled trials. Since we were specifically interested in the quality of pharmacokinetic model analyses and the reporting of the modeling outcome, we developed a new set of criteria, with special focus on aspects that are important for modelling. We adjudicated the following items: (i) data reporting, (ii) statistical approach, (iii) model diagnostics, (iv) analytical assay and (v) sampling scheme reporting. The assay is relevant as its quality may have a large impact on the outcome of the data sample values and consequently on the model outcome. Each item was assigned a numerical rating based on the quality of that specific field. The adjudication points were given as follows:

(i) Data reporting adjudication points: 0, in case of absence of raw or mean PK data reporting; 1, when individual or mean concentrations *versus* time are reported in tables or graphs.

(ii) Statistical approach adjudication points: 0, when a two-stage analysis approach (mean PK parameters are calculated from individually performed PK data fits) is performed; 1, in case of an iterated two-stage approach; or 2, when a mixed-effects analysis (analysis allowing estimation of within and between-subject variability) is performed. The distinction between the latter two methods is a difference in optimization algorithm.

(iii) Model diagnostics adjudication points: 0, when no model diagnostics; 1, simple diagnostics; 2, basic diagnostics; or 3 advanced diagnostics are reported. Diagnostics were considered "simple" when visual inspection of one model fit was used to evaluate model performance. Diagnostics were considered "basic" when one of the following was reported: observed *versus* predicted plot, residual plot, worst/median/best fit plots, visual predictive check (VPC) or bootstrap analysis. Diagnostics were considered "advanced" when at least 2 of these diagnostic plots were reported.

(iv) Analytical assay adjudication points: 0, in case the analysis technique is not reported; or 1, when the analysis technique and quality is presented in the text.

(v) Sampling scheme reporting adjudication points: 0, when no blood sampling times and/or no sampling duration after the last dose was reported or could be deduced otherwise; or 1, when a sampling scheme was reported or could be deduced otherwise.

A maximum of 8 adjudication points could be assigned per study.

Data extraction

Study population characteristics, administration route, administered ketamine formulation, sampling site (arterial or venous), model characteristics, measured analytes (*RS*-ketamine, *R*-ketamine or *S*-ketamine), pharmacokinetic parameter estimates, method of analysis and model diagnostics were extracted from the included papers. To be able to compare PK parameters from different models, the original parameter nomenclature was adapted, where possible, to a uniform notation. Furthermore, original parameter values were recalculated to uniform pharmacokinetic parameter units. To allow comparisons among studies, we calculated standardized ketamine (and norketamine, if possible) parameters. We allometrically scaled volume of distribution to L per 70 kg and clearance to L/h at 70 kg by applying the following formulas: compartmental volume of distribution (*i.e.* the sum of central and peripheral compartment volumes) = $V_{REPORTED}$ × (70/body weight) and standardized clearance = $CL_{REPORTED}$ × (70/body weight)$^{0.75}$, where $V_{REPORTED}$ and $CL_{REPORTED}$ are the corresponding parameters originally reported in the papers.

Standard errors of the parameter estimates were extracted from the included papers or calculated, where possible, from standard deviations. To allow for the comparison of the parameter estimate precision between studies, the standard errors were converted into coefficients of variation. The statistical software package R version 4.0.2 for mac OS (R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) was used for parameter recalculation. After parameter extraction and standardization, the meta-analyses were performed.

Meta-analyses

Weighted means for ketamine volume of distribution, clearance and norketamine volume of distribution and clearance were calculated from studies that performed a population mixed-effects analysis. This was done to overcome the bias of the outcome from studies that used a two-stage analysis. Models were excluded when no parameter standard errors were reported, when the model was based on mixed adult and pediatric data and when parameters were considered to be outliers. Outliers were *a priori* somewhat arbitrarily defined as volume of distribution > 1000 L/70 kg and clearance > 200 L/h (at 70 kg).

Weighting of the parameters was performed according to the following equation: $W = 1 / (\sigma^2 + \tau^2)$, in which W is the weight assigned to each individual population parameter, σ^2 is the within-study variance and τ^2 the estimated between-study variance. Total rating from the quality assessment was included as additional weight. Maximum likelihood estimation was used to estimate inter-study variability. The meta-analysis was performed in R using the metafor package version 2.1-0.[7] Effects of study characteristics (*e.g.* ketamine formulation, analyte enantiomer, population size, sampling site, healthy *versus* patient and adult *versus* pediatric population) were evaluated by automated covariate selection in R (glmulti package version 1.0.7.1.),[7] based on the small-sample corrected Akaike information criterion.

In addition, we constructed a 3-compartment meta-analytical ketamine model, partially based on a meta-analytical method published previously.[8] Only studies that analyzed the data with a three-compartment mixed-effects population model were included for this analysis. Models were excluded when no parameter standard errors were reported. The parameters were calculated by determining the mean weighted value for each parameter in the three-compartmental model (*e.g.* elimination clearance, two intercompartmental clearances, central volume of distribution and two peripheral volumes of distribution). Calculation of the mean weighted parameters was performed in a similar way as the mean weighted volume of distribution and clearance parameters, as described above.

Population analysis: nonlinear mixed-effects modeling

Raw data sets already in our possession and 8 sets from the literature that were kindly shared by our contributors, were standardized to time in minutes and ketamine concentrations in ng/mL. Two and three compartmental ketamine models were tested. To account for differences in arterial *versus* venous sampling, adding one or two arm compartment(s) was tested. Data analysis was performed in NONMEM 7.5 beta version 4 (ICON Development Solutions, Hanover, Maryland). Three potential sources of variability were identified: (i) inter-individual variability (IIV), (ii) inter-occasion variability (IOV) and (iii) inter-study variability (ISV). To include ISV in the model, the $LEVEL option (the improved method as available in the beta version of NONMEM) was used. An exponential relation was used to account for the random effects: $\theta_i = \theta \exp(\eta_{IIV} + \eta_{IOV} + \eta_{ISV})$, where θ_i is the parameter for individual i, θ the population parameter, η_{IIV} is the random difference between the population and individual parameter, η_{IOV} the difference due to inter-occasion variability and η_{ISV} the difference due to inter-study variability. Because very few studies had more than one occasion, the analysis was simplified by treating data obtained on different occasions (from one subject) as different subjects. The stochastic approximation expectation-maximization algorithm in combination with importance sampling was used to estimate the model parameters. Model selection was based on significant decreases of the objective function value, calculated in NONMEM as -2LogLikelihood (χ^2-test, with $p < 0.01$ considered significant).

Since differences in pharmacokinetics may be expected between adult and pediatric populations, volume of distribution, clearance and half-times of the venous compartments were allometrically scaled. Because the volumes of the PK compartments were correlated, these were parameterized as fractions of the total volume of distribution. The number of variability terms to be estimated was sequentially increased to obtain minimal but stable final objective function values of the stochastic approximation expectation-maximization step by observing their shrinkages, recognizing that some studies had rather sparse sampling. Next, possible remaining covariate effects were explored in an automated procedure by Perl speaks NONMEM's stepwise covariate model building utility. The potential effects of ketamine administration form, enantiomer analyzed, health status, sex and pediatric *versus* adult on ketamine pharmacokinetics were tested in a stepwise fashion. A criterion of $p < 0.01$ was used for the forward selection, after which a more stringent criterion of $p < 0.001$ was used for the backward covariate selection.

Simulations

The standardized pharmacokinetic parameters derived from the meta-analysis were used to simulate concentration-time profiles to assess the time to steady state, context sensitive half-times and wash-in/wash-out profiles following a bolus infusion for

each study. Time to steady-state was defined as the time needed to achieve 90% of a theoretical steady-state concentration of 1 (arbitrary units) with an infusion rate equal to the elimination clearance times the theoretical steady-state concentration. Context-sensitive half-time was defined as the time needed to reach 50% of the maximum concentration after different zero-order infusion durations (10 and 30 min and 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hours).

Finally, simulations were performed using mean and typical parameter values to compare the output of the meta-analytical three-compartment meta-analytical model and the output of the combined pharmacokinetic analysis of the raw data sets. Different scenarios were simulated: (1) A 40-min infusion of 0.5 mg/kg esketamine with *S*-ketamine measured; (2) 40-min infusion of 0.5 mg/kg racemic ketamine with *S*-ketamine measured; and (3) a 40-min infusion of 0.5 mg/kg racemic ketamine with *R*-ketamine measured. All simulations were performed in R using the RxODE package version 0.8-0.9.

RESULTS

Literature search strategy and selection

The literature search resulted in 1,285 records from the Pubmed, Embase and Web of science databases, respectively (Fig. 1). After removal of 321 duplicates, the title and abstracts of 964 papers were screened. This resulted in 49 eligible articles that were selected for full-text screening. Twenty-five papers were excluded after full-text reading because of various reasons (*e.g.* insufficient data for parameter standardization, animal study, review paper). Five additional papers were included after screening of the text and references of the initial 24 included papers. Finally, one pharmacokinetic analysis from an earlier published descriptive study was included. [9,10]

Systematic review

The systematic review was performed on 30 individual studies that included a total of 823 individuals (Table 1). The median number of subjects per study was 27 with interquartile range 11-34 and range 5-113. The majority of studies were performed exclusively in healthy volunteers of either sex (n = 14), followed by adult patients (n = 9) and pediatric patients (n = 6). Additionally, two studies included both pediatric patients and (healthy and/or diseased) adults; one study included both healthy and diseased adults. The racemic mixture was administered in 18 studies, the *S*-enantiomer in 13-studies and the *R*-enantiomer in one study; in four studies multiple formulations were tested. The route of administration was intravenous (n = 28), oral or through a gastric tube (n = 2), intramuscular (n = 4), intranasal (n = 1) or inhalational (n = 1), with

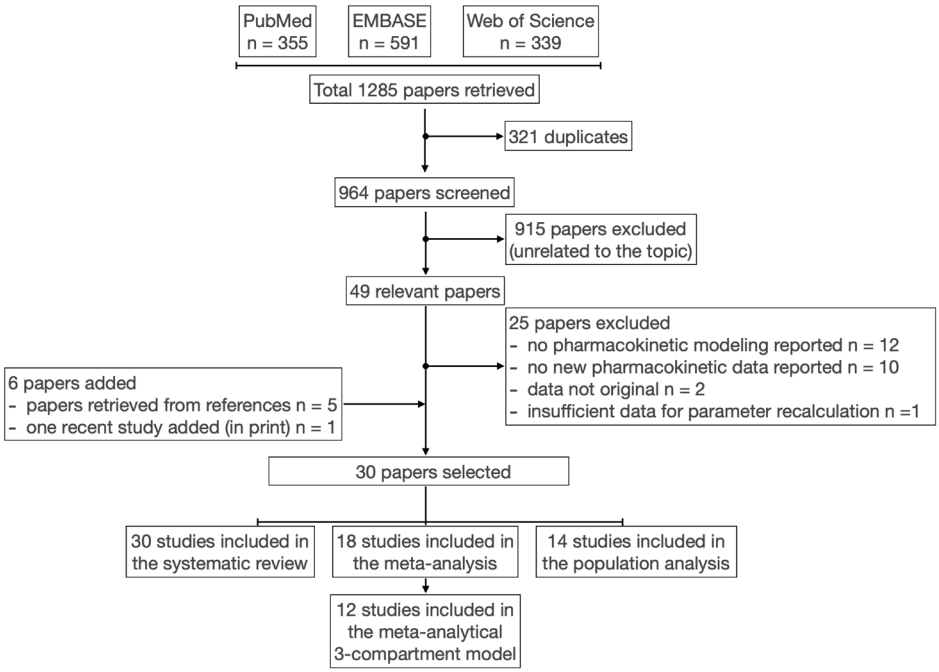

Figure 1. Schematic overview of the literature selection and performed analyses.

several studies investigating more than one route of administration. In 9 studies, blood samples were arterial, in 19 venous and in one study samples were either arterial or venous depending on the port that was available in the patient, and finally in one study simultaneous venous and arterial samples were obtained.

Quality assessment

Figure 2 gives the total quality assessment of each study and the scores per adjudication item. In the early publication years, 1981-2006, the quality scores of the studies were relatively poor with scores ranging from 1 to 5 (Fig. 2C). This was related to low scores for all 5 adjudication categories: data reporting, statistical approach, model diagnostics, analytical assay and sampling scheme reporting. From 2007 on the quality scores improved to values ranging from 6-8 in 19/20 studies. There was no correlation between the number of subjects in the study and the quality scores.

Description of studies

We here give a brief narrative of the included studies. The studies are arranged according to publication date. Parameter estimates are given in Table 1, quality scores in Figure 2.

Table 1. Study characteristics and (recalculated) model estimates, volume of distribution and Clearance.

Author	Year	Population	Number of participants	Administration Route	Sample Site	Input → Output	Volume of distribution ± standard error of estimate (L/70 kg)	% coefficient of variation	Clearance ± standard error of estimate (L/h per 70 kg)	%coefficient of variation
Clements	1981	Healthy adults	5	intravenous	venous	Racemic ketamine → *RS*-ketamine	182 ± 18	10	76 ± 4	5
Clements	1982	Healthy adults	5	intravenous	venous	Racemic ketamine → *RS*-ketamine	359 ± 26	7	82 ± 5	6
			6	intramuscular	venous	Racemic ketamine → *RS*-ketamine	363 ± 51	14	98 ± 11	12
Domino	1982	Surgical patients	5	intravenous	venous	Racemic ketamine → *RS*-ketamine	162 ± 39	24	83 ± 15	17
Domino	1984	Healthy adults	7	intravenous	venous	Racemic ketamine → *RS*-ketamine	124 ± 17	14	60 ± 8	14
Geisslinger	1995	Surgical patients	21	intravenous	venous	*S*-ketamine → *S*-ketamine	206 ± 31	15	74 ± 6	7
			24	intravenous	venous	Racemic ketamine → *S*-ketamine	236 ± 18	8	87 ± 7	8
						Racemic ketamine → *R*-Ketamine	212 ± 18	9	78 ± 5	6
Ihmsen[1,3]	2001	Healthy adults	10	intravenous	arterial	*S*-ketamine → *S*-ketamine	189 ± 41	21	114 ± 15	13

Table 1. Study characteristics and (recalculated) model estimates, volume of distribution and Clearance. (continued)

Author	Year	Population	Number of participants	Administration Route	Sample Site	Input → Output	Volume of distribution ± standard error of estimate (L/70 kg)	% coefficient of variation	Clearance ± standard error of estimate (L/h per 70 kg)	%coefficient of variation
						Racemic ketamine → *RS*-ketamine	153 ± 53	35	64 ± 7	11
						Racemic ketamine → *S*-ketamine	201 ± 38	19	80 ± 3	4
						Racemic ketamine → *R*-ketamine	94 ± 43	45	60 ± 6	9
Hijazi	2003	ICU patients	12	intravenous	arterial	Racemic ketamine → *RS*-ketamine	379 ± 129	34	87 ± 24	28
Hijazi	2003	ICU patients	6	intravenous	arterial	Racemic ketamine → *RS*-ketamine	507 ± 165	33	122 ± 35	29
White	2006	Patients under propofol for colonoscopy	20	intravenous	venous	*S*-ketamine → *S*-ketamine	68 ± -	-	172 ± -	-
Herd[1,4]	2007	Pediatric patients (1.5-14 years)	54	intravenous	venous	Racemic ketamine → *RS*-ketamine	140 ± 13	9	90 ± 9	10
Herd	2007	Mixed pediatric (patient) and adult population	57 children 13 adults	intravenous or intramuscular	venous	Racemic ketamine → *RS*-ketamine	151 ± 40	26	60 ± 28	47
						Racemic ketamine → *RS*-norketamine	22 ± 7	30	14 ± 15	109

Table 1. Study characteristics and (recalculated) model estimates, volume of distribution and Clearance. (continued)

Author	Year	Population	Number of participants	Administration Route	Sample Site	Input → Output	Volume of distribution ± standard error of estimate (L/70 kg)	% coefficient of variation	Clearance ± standard error of estimate (L/h per 70 kg)	%coefficient of variation
Sigtermans[1,2,3,4]	2009	Healthy males and females	10 men 10 women	intravenous	arterial	*S*-ketamine → *S*-ketamine	145 ± 8	5	75 ± 5 (men) 97 ± 3 (women)	6 3
						SI-ketamine → *S*-norketamine	178 ± 12	7	53 ± 5 (men) 79 ± 6 (women)	9 7
Brunette	2011	Pediatric patients combined with data from the literature (adults/ children)	91	intravenous, intramuscular or oral	venous	Racemic ketamine → *RS*-ketamine	130 ± 15	11	83 ± 8	10
						Racemic ketamine → *RS*-norketamine	152 ± 63	41	64 ± 10	16
Dahan[1,2,4]	2011	CRPS T1 patients	30	intravenous	venous	*S*-ketamine → *S*-ketamine	560 ± 91	16	83 ± 6	7
						S-ketamine → *S*-norketamine	53 ± 8	14	26 ± 2	9
Noppers[1,2,3,4]	2011	Healthy volunteers	20	intravenous	arterial	*S*-ketamine → *S*-ketamine	192 ± 11	6	94 ± 3	3
						S-ketamine → *S*-norketamine	210 ± 65	5	65 ± 3	4

Table 1. Study characteristics and (recalculated) model estimates, volume of distribution and Clearance. (continued)

Author	Year	Population	Number of participants	Administration Route	Sample Site	Input → Output	Volume of distribution ± standard error of estimate (L/70 kg)	% coefficient of variation	Clearance ± standard error of estimate (L/h per 70 kg)	%coefficient of variation
Goldberg	2011	CRPS T1 patients	16	intravenous	venous	Racemic ketamine → *S*-ketamine	65 ± -	-	64 ± -	-
						Racemic ketamine → *S*-norketamine	65 ± -	-	55 ± -	-
						Racemic ketamine → *R*-ketamine	59 ± -	-	59 ± -	-
						Racemic ketamine → *R*-norketamine	59 ± -	-	41 ± -	-
Olofsen[1,3,4]	2012	CRPS T1 patients	10	intravenous	arterial	*S*-ketamine → *S*-ketamine	193 ± 21	11	-	-
		Healthy volunteers	12				153 ± 16	10	-	-
		Females (mixed)	16				-	-	86 ± 3	4
		Males (healthy)	6				-	-	78 ± 6	8
		Females (patient)	10				-	-	-	-
		Females (healthy)	6				-	-	-	-
		Males (healthy)	6				-	-	-	-
Zhao[1,2]	2012	Patients with bipolar depression	9	intravenous	venous	Racemic ketamine → *S*-ketamine	2,205 ± 1,394	63	18 ± 2	12
						Racemic ketamine → *S*-norketamine	49 ± 2	4	12 ± 1	10

Table 1. Study characteristics and (recalculated) model estimates, volume of distribution and Clearance. (continued)

Author	Year	Population	Number of participants	Administration Route	Sample Site	Input → Output	Volume of distribution ± standard error of estimate (L/70 kg)	% coefficient of variation	Clearance ± standard error of estimate (L/h per 70 kg)	%coefficient of variation
						Racemic ketamine → *R*-ketamine	196 ±22	11	655 ± 20	2
						Racemic ketamine → *R*-norketamine	82 ± 19	23	26 ± 3	12
Nielsen[1,2]	2013	Pediatric patients (0.8-17 years)	13	intravenous	venous	Racemic ketamine → *RS*-ketamine	156 ± 13	8	63 ± 18	28
						Racemic ketamine → *RS*-norketamine	24 ± 5	22	8 ± 6	80
Elkomy[1,4]	2015	Pediatric patients (0.67-16 years)	21	intravenous	venous	Racemic ketamine → *RS*-ketamine	209 ± 22	11	61 ± 5	8
Sherwin	2015	Pediatric patients (data from Herd)	57	intravenous	venous	Racemic ketamine → *RS*-ketamine	108 ± 36	33	87 ± 46	53
Fanta[1,2,3,4]	2015†	Healthy adults	12	intravenous and oral	venous	*S*-ketamine → *S*-ketamine	419 ± 136	33	95 ± 6	6
						S-ketamine → *S*-norketamine	278 ± 20	7	54 ± 3	6
Khalili[1,4]	2015	Healthy adults	12	intravenous	venous	*S*-ketamine → *S*-ketamine	196 ± 10	5	132 ± 6	5

Table 1. Study characteristics and (recalculated) model estimates, volume of distribution and Clearance. (continued)

Author	Year	Population	Number of participants	Administration Route	Sample Site	Input → Output	Volume of distribution ± standard error of estimate (L/70 kg)	% coefficient of variation	Clearance ± standard error of estimate (L/h per 70 kg)	%coefficient of variation
Flint[1,2,4]	2017	Pediatric patients (0.02-12.5 years)	25	intravenous	venous or arterial	*S*-ketamine → *S*-ketamine	552 ± 104	19	112 ± 10	9
						S-ketamine → *S*-norketamine	1 (fix)	-	104 ± 14	13
Jonkman[1,2,3]	2017	Healthy adults	19	intravenous and inhaled	arterial	*S*-ketamine → *S*-ketamine	199 ± 16	8	89 ± 5	5
						S-ketamine → *S*-norketamine	90 ± 22	24	57 ± 15	26
Ashraf[1,2,3,4]	2018	Healthy adults	56	intravenous	venous	*S*-ketamine → *S*-ketamine	328 ± 14	4	93 ± 15	16
Hornik[1,4]	2018	Pediatric patients (0.02-17.6 years)	113	intravenous	venous	Racemic ketamine → *RS*-ketamine	185 ± 56	30	39 ± 6	15
Jonkman[1,3,4]	2018	Healthy adults	12	intravenous	arterial	*S*-ketamine → *S*-ketamine	159 ± 8	5	90 ± 3	3
Henthorn[1,3,4]	2018	Healthy adults	10	intravenous	venous and arterial	*S*-ketamine → *S*-ketamine	518 ± 20	4	70 ± 2	3
						R-ketamine → *R*-ketamine	518 ± 20	4	60 ± 2	3

Table 1. Study characteristics and (recalculated) model estimates, volume of distribution and Clearance. (continued)

Author	Year	Population	Number of participants	Administration Route	Sample Site	Input → Output	Volume of distribution ± standard error of estimate (L/70 kg)	% coefficient of variation	Clearance ± standard error of estimate (L/h per 70 kg)	%coefficient of variation
Kamp[1,2,4]	2019	Healthy adult	20	intravenous	arterial	Racemic ketamine → *S*-ketamine	189 ± 10	5	99 ± 4	4
						Racemic ketamine → *R*-ketamine	181 ± 10	6	89 ± 4	4
						S-ketamine → *S*-ketamine	189 ± 10	5	99 ± 4	4

[1] included in the ketamine meta-analysis (n = 18 studies); [2] included in norketamine meta-analysis (n = 10 studies);[3] included in the three-compartment meta-analytical pharmacokinetic model (n = 9 studies); [4] included in the raw data pharmacokinetic model (n = 14 studies).

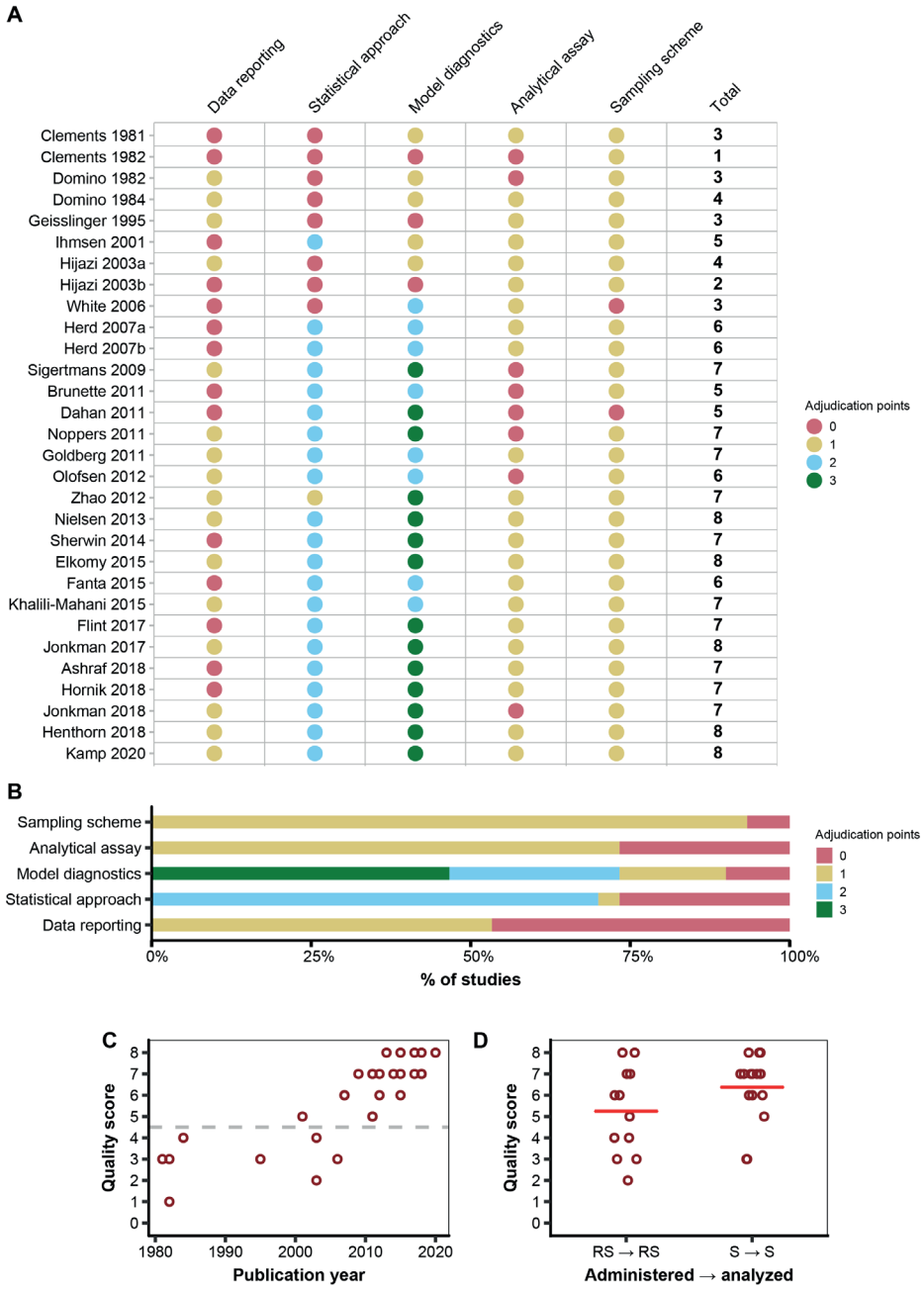

Figure 2. Adjudication of the extracted studies. Adjudication points given for data reporting, statistical approach, model diagnostics, analytical assay, sampling scheme for each of the included studies (**A**), overall distribution of study quality (**B**), study quality scores over the years (**C**) and quality scores for studies that administered racemic ketamine and measured racemic ketamine in plasma and studies that administered the S-enantiomer and measured S-ketamine in plasma (**D**). The bars indicate mean values.

Study 1. The first ketamine PK model analysis is published in 1981 by Clements and Nimmo.[11] The authors studied the effect of *RS*-ketamine in 5 healthy adults by intravenous route and measured *RS*-ketamine concentrations from venous plasma. Ketamine's PK data were best described by a two-compartment model.

Study 2. In this study, published in 1982, Clements et al.[12] administered *RS*-ketamine to 5 healthy adult volunteers by intravenous, and to 6 others by intramuscular route with *RS*-ketamine venous sampling. This is the only study with a total quality score of 1 due to absence of relevant information on data reporting, statistical approach, model diagnostics or analytical assay. The authors also studied the oral administration of RS-ketamine but did not provide sufficient information for accurate estimation of Vd and CL. A two-compartment model was used to describe ketamine pharmacokinetic data. However, only total body clearance and total volume of distribution were reported.

Studies 3 and 4. Domino et al. (1982 and 1984) injected *RS*-ketamine to seven premedicated surgical patients,[13] and seven healthy inmates at the Jackson State Prison (Michigan),[14] following diazepam or saline infusion and measured *RS*-ketamine concentrations from venous plasma. Here, we only report the data from the saline treated group. Both papers reported a three-compartment open model to describe the ketamine pharmacokinetic data.

Study 5. Geisslinger et al.[15,16] (1995) administered *S*-ketamine and *RS*-ketamine to 21 and 24 surgical patients, respectively, during anesthesia induction (midazolam/rocuronium). They measured the two enantiomers in venous plasma. Study Ref. 14 is a reanalysis of an earlier publication (Ref. 15) and was used in the meta-analysis. No differences in pharmacokinetics between pure S-ketamine and *S*-ketamine after racemate administration were observed. However, in the racemate group *S*-ketamine showed a higher clearance and volume of distribution compared to the *R*-ketamine. The authors described ketamine pharmacokinetic data with a three-compartment model.

Study 6. Ihmsen et al.[17] studied ten healthy volunteers and administered *RS*- and *S*-ketamine on two occasions using a target-controlled infusion (TCI) system with linear increasing plasma concentration targets. *RS*-ketamine and both enantiomers were measured from arterial plasma. The results suggest that the *R*-enantiomer inhibits the elimination of the *S*-enantiomer. A three-compartment model was used to describe the ketamine pharmacokinetic data.

Studies 7 and 8. In two separate studies, Hijazi et al.[18,19] administered *RS*-ketamine in 12 (2003a) and six (2003b) patients admitted to the intensive care with brain or spinal cord injury. *RS*-ketamine was determined from arterial blood samples. In both studies, a two-compartment model was used to fit the ketamine pharmacokinetic data.

Study 9. Using a target-controlled infusion paradigm, White et al.[20] (2006) administered *S*-ketamine, in combination with propofol, to 20 patients undergoing a colonoscopy.

S-ketamine was measured from venous plasma. The authors used a three-compartment model, that was partially based on a previously published model.[15]

Studies 10 and 11. Herd et al. evaluated *RS*-ketamine PK in two studies.[21,22] In the first study (2007a), they administered intravenous *RS*-ketamine to 54 children that underwent a painful procedure in the emergency department. In the second study (2007b), they combined experimental data obtained from two sources: experimental data from the first study (2007a) and literature time-concentration data from 16 adults and children on either intravenous or intramuscular *RS*-ketamine. They determined both *RS*-ketamine and *RS*-norketamine pharmacokinetic parameter estimates from venous plasma. Both studies used a two-compartment model to describe the ketamine pharmacokinetic data. In addition, the second study described the norketamine pharmacokinetic data with a one compartment model that was linked to the central ketamine compartment via 3 metabolic compartments.

Study 12. As part of a pharmacokinetic-pharmacodynamic modeling study, Sigtermans et al.[23] (2009) studied the effect of sex on the pharmacokinetics of *S*-ketamine and *S*-norketamine following a 2-h linearly increasing *S*-ketamine infusion in 10 male and 10 female healthy adults. Samples were obtained from an arterial line. *S*-ketamine and *S*-norketamine clearances were 20% greater in female volunteers. Three- and two-compartment models were used to describe the ketamine and norketamine pharmacokinetic data, respectively. The ketamine and norketamine central compartments were linked by a series of 3 metabolic compartments. The model incorporated ketamine elimination clearance and a separate ketamine clearance responsible for norketamine formation.

Study 13. Brunette et al.[24] (2011) studied the effect of *RS*-ketamine in a population of 20 pediatric patients just before sevoflurane anesthesia for a procedure related to acute burn injury (>10% body surface area). The ketamine was administered via a nasogastric tube and nine children received additional intravenous injections. The pharmacokinetic data were pooled with 70 data sets from earlier studies in adults and children on intravenous or intramuscular *RS*-ketamine and with data from one additional adult subject after oral ketamine. Blood sampling for *RS*-ketamine and *RS*-norketamine was from venous blood. Ketamine and norketamine pharmacokinetic data were described by two- and one compartment models, respectively. Norketamine formation was modeled by three metabolic compartments. In addition, depot compartments were incorporated for intramuscular (1 compartment) and oral (2 compartments) administration. A first pass compartment linked to one of the oral depot compartments accounted for the norketamine formation due to first pass metabolism. For the final model, it was assumed that ketamine was completely converted to norketamine.

Study 14. Dahan et al.[2] (2011) treated 30 patients with complex regional pain syndrome type 1 for 100 h with *S*-ketamine and measured venous *S*-ketamine and *S*-

norketamine concentrations for 108 h. A two- and one compartment model were used to describe the ketamine and norketamine pharmacokinetic data, respectively. The ketamine fraction converted to norketamine was incorporated in this model.

Study 15. In 20 healthy volunteers, Noppers et al.[25] (2011) examined the effect of CYP enzyme induction by rifampicin *versus* placebo on the pharmacokinetics of *S*-ketamine and *S*-norketamine (measured in arterial blood). Here we present just the placebo data. The compartmental model used to describe the ketamine and norketamine pharmacokinetic data were identical to that of study of Sigtermans et al. (see study #12).

Study 16. In 16 patients with complex regional pain syndrome type 1, Goldberg et al.[26] (2011) infused *RS*-ketamine for 5 days and measured venous *S*- and *R*-ketamine and norketamine for 5 days. *R*-ketamine clearance was lower than *S*-ketamine clearance. A one compartmental model was used to describe both ketamine and norketamine pharmacokinetic data.

Study 17. In 10 chronic pain patients (diagnosed with complex regional pain syndrome type 1) and 12 healthy volunteers, Olofsen et al.[27] (2012) studied the pharmacokinetics of *S*-ketamine (measured in arterial blood) as part a study of the effect of ketamine on cardiac output. A three compartmental model with small differences in parameter estimates between healthy and diseased participants and men and women was used to describe the ketamine pharmacokinetic data.

Study 18. Zhao et al.[28] (2012) studied the pharmacokinetic effect of *RS*-ketamine in nine patients with treatment-resistant bipolar depression and modelled venous *S*- and *R*- ketamine, norketamine, dehydronorketamine and hydroxynorketamine concentrations. We here present the ketamine and norketamine parameter estimates. Outliers were observed for *S*-ketamine Vd and *R*-ketamine CL. Ketamine pharmacokinetic data were described by a three-compartment model; a two-compartment model was used to describe the norketamine data and one-compartment models were used to describe dehydronorketamine and hydroxynorketamine pharmacokinetic data.

Study 19. Nielsen et al.[29] (2014) studied the effect of intranasal *RS*-ketamine combined with sufentanil in 50 pediatric patients admitted in the hospital for a painful procedure. In 13 of these patients, venous samples were obtained for the measurement of *RS*-ketamine, *RS*-norketamine and sufentanil. A two-compartment linear disposition model was used to describe the ketamine data. Norketamine data were described by a one-compartment model. Central parent and metabolite compartments were linked by a series of intermediate metabolic compartments (number of metabolic compartments not reported). Furthermore, the model included a separate ketamine elimination clearance and ketamine clearance responsible for norketamine formation.

Study 20. Elkomy et al.[30] (2015) administered *RS*-ketamine to 20 children with congenital heart disease during inhalational anesthesia for surgery. Venous blood samples

for *RS*-ketamine measurement were drawn during and following the procedure. A-two compartmental model was used to describe the ketamine pharmacokinetic data.

Study 21. Sherwin et al.[31] (2015) reanalyzed the data of Herd et al. (2007b) obtained from 57 pediatric patients to develop an optimal sampling schedule. Since the authors used a Bayesian analysis approach in contrast to the original analysis, we included their analysis in the review. The ketamine pharmacokinetic data were modelled with a two compartment model.

Study 22. Fanta et al.[32] (2015) administered *S*-ketamine by intravenous or oral route on two occasions to 12 healthy volunteers; venous *S*-ketamine and norketamine concentrations were measured. Both ketamine and norketamine pharmacokinetic data were described by a three-compartment model. To model norketamine formation from ketamine, the central ketamine and norketamine compartments were linked via a series of three metabolic compartments. Furthermore, an oral absorption compartment for ketamine was included, with three preceding ketamine absorption transit compartments. Finally, an absorption compartment with four preceding norketamine absorption transit compartments was included to account for the conversion of orally dosed ketamine to norketamine during first-pass metabolism and absorption.

Study 23. Khalili-Mahani et al.[33] (2015) studied the influence of *S*-ketamine on cortisol levels in 12 healthy adults; venous *S*-ketamine concentrations were modelled. The ketamine pharmacokinetic data were modeled with a one-compartment model.

Study 24. Flint et al.[34] (2017) studied the pharmacokinetics of *S*-ketamine in a pediatric population requiring long-term sedation in the pediatric intensive care unit. *S*-ketamine combined with lorazepam was administered for 5 days to 25 children as part of a sedation rotation schedule. Blood was sampled for *S*-ketamine and norketamine concentrations from an arterial or a venous line, depending on the availability. Ketamine and norketamine data were described by two- and one-compartment models, respectively. In addition, norketamine formation was estimated as a fraction of the ketamine clearance.

Study 25. Jonkman et al.[35] (2017) studied the pharmacokinetics of intravenous and inhaled nebulized *S*-ketamine in 19 healthy volunteers and measured arterial *S*-ketamine and norketamine concentrations. Nebulized ketamine had a substantial reduction in bioavailability (possibly related to particle retention and drug loss in the air). The three compartmental model was based on that of Sigtermans et al. (study #12). However, to account for absorption after ketamine inhalation, bioavailability and a direct and delayed absorption pathway were included. The direct absorption pathway was modeled as fraction φ of the available ketamine, after correcting for bioavailability. The delayed pathway was modeled as fraction $1 - \varphi$ that first went into a delay compartment, after which it was finally absorbed with rate constant k.

Study 26. Ashraf et al.[36] (2018) used the concentration-time data from 5 previous studies to determine the effect of the CYP enzyme inhibitor ticlopidine *versus* placebo on venous *S*-ketamine and norketamine pharmacokinetics. Here we report the placebo data. The ketamine and norketamine pharmacokinetic data were best described by three- and two-semi-mechanistic compartment models, respectively, that enabled description of intrinsic hepatic and gut clearance of ketamine and norketamine.

Study 27. Hornik et al.[37] (2018) studied *RS*-ketamine administered *via* the intramuscular and intravenous routes in two separate studies that were part of the Pediatric Trials Network's *Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care* trial. Venous *RS*-ketamine samples were obtained in 113 children. The pharmacokinetic data were described by a two-compartmental model with a parameter for bioavailability following intramuscular administration. Furthermore, the model included extracorporeal membrane oxygenation (ECMO) as covariate on ketamine clearance.

Study 28. Jonkman et al.[3] (2018) studied the effect of the *S*-ketamine on respiratory depression induced by remifentanil in 12 healthy volunteers. Arterial *S*-ketamine concentrations were obtained during remifentanil administration and on a separate occasion when no opioids were administered. The *S*-ketamine pharmacokinetic data were described by a three-compartment model.

Study 29. Henthorn et al.[38] (2018) administered *R*- and *S*-ketamine to 10 healthy volunteers on separate occasions and took arterial and venous blood samples. A model with arterial mixing and venous blood components was constructed to analyze the arterial and venous data simultaneously. The model included an unmixed compartment in which the drug was infused. The drug was then cleared to the central compartment by the pharmacokinetic flow, equal to the cardiac output, corrected for hematocrit and the red blood cell/plasma partitioning of the drug. In addition, the authors added an arm compartment to approximate mixed venous drug concentrations.

Study 30. Kamp et al.[9] (2019) performed a pharmacokinetic analysis of earlier published data[10] on the influence of the nitric oxide donor sodium nitroprusside on *S*-ketamine and *RS*-ketamine pharmacodynamics. In 20 volunteers both formulations were administered on separate occasions and the concentrations of *R*- and/or *S*-ketamine and metabolites (norketamine, dehydronorketamine and hydroxynorketamine) were measured in arterial plasma. A multi-compartment model (2 compartments for ketamine, 1 for norketamine, 1 for dehydronorketamine and 2 for hydroxynorketamine), including weight as covariate on all parameters and ketamine enantiomer as covariate on ketamine CL and V2, best described the data.

Meta-analyses

Ketamine

Twenty-two studies that performed a mixed-effects analysis were identified**.** The parameter estimates published by Herd et al.[22], Brunette et al.[24] and Sherwin et al.[31] were excluded from all meta-analyses since the estimates were derived from mixed pediatric and adult study populations. Additionally, the estimates from the study of Goldberg et al.[26] were excluded due to absence of standard errors. Therefore, eighteen studies were included in the meta-analysis. To determine the average weighted volume of distribution, we excluded the study of Zhao et al.[28] because of high values.

The population weighted mean volume of distribution value was 252 L/70 kg (95% confidence interval 200 - 304 L/70 kg). Equivalent values for clearance were 79 L/h at 70 kg (69-90 L/h at 70 kg). A sensitivity analysis revealed that no single study could be considered an outlier (% coefficient of variation = 3.4% and 2.0% for volume of distribution and clearance, respectively, in a leave-one-out method).

We subdivided the studies that administered *S*- or *RS*-ketamine per study population (adult healthy volunteers, adult patients, pediatric patients), formulation administered (*RS*-ketamine (RSK), *S*-ketamine (SK)), analyte (RSK, SK, *R*-ketamine (RK)), and sampling site (arterial, venous). No obvious differences in weighted means of volume of distribution among subgroups were observed. For clearance, while the mean values differed up to 35% between *S*-ketamine following *S*-ketamine administration and *R*-ketamine following racemic ketamine administration, in healthy adults ($p < 0.01$), meta-regression analysis, performed on the complete data set, however, revealed that none of the covariates contributed significantly to the model, according to Akaike's criterion.

We identified 10 papers reporting three-compartment population models. Due to the occurrence of outliers, the data from Zhao et al.[28] were excluded. Studies included in the three-compartment meta-model, are indicated in Table 1. The mean weighted pharmacokinetic parameters for the three-compartment meta-analytical model are given in Table 2.

Norketamine

Just a subset of studies (13/30) measured norketamine concentrations and took this metabolite into account in their population pharmacokinetic model. No evident outliers were observed. As described above, Brunette et al., Herd et al. and Goldberg et al. were excluded because of the mixed pediatric and adult populations or lacking standard errors.[22,24,26] Flint et al.[34] was excluded from the volume of distribution analysis because the norketamine volume of compartment 1 (V1) was fixed at 1. The weighted mean volume of distribution equaled 142 L/70 kg (95% confidence interval 87-298 L/70 kg). Equivalent values for clearance were 48 L/h at 70 kg, (33-63 L/h at 70 kg). We refrained from reporting subgroup data as the subgroups were rather small and no obvious differences between any subgroups were detectable.

Table 2. Pharmacokinetic parameters of the 3-compartment meta-analytical model

Parameter	Mean estimate ± relative standard error	τ ± relative standard error
CL (L/h at 70 kg)	84 ± 3	11 ± 7
Q2 (L/h at 70 kg)	161 ± 22	71 ± 47
Q3 (L/h at 70 kg)	79 ± 11	37 ± 25
V1 (L per 70 kg)	25 ± 7	25 ± 17
V2 (L per 70 kg)	56 ± 15	36 ± 24
V3 (L per 70 kg)	157 ± 19	62 ± 41

CL = elimination clearance; Q2 and Q3 = intercompartmental clearances; V1 = central compartment volume; V2-V3 = peripheral compartment volumes; τ = interstudy variability with the same unit as the parameter; unit of relative standard error is %.

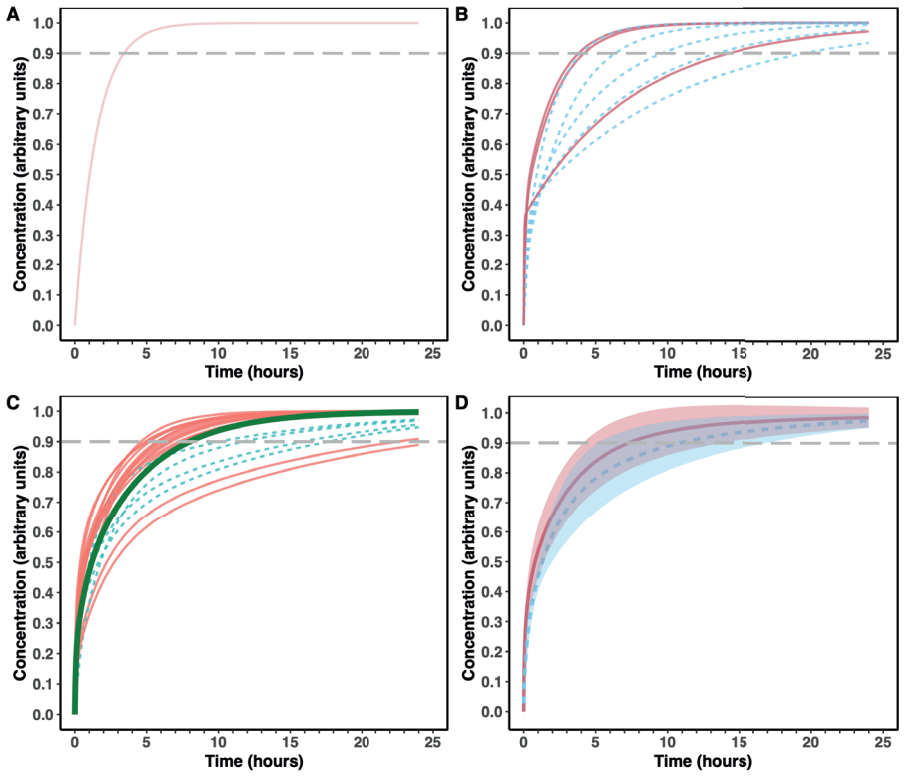

Figure 3. Simulations of the ketamine arterial (red) and venous (blue) plasma concentrations following the start of ketamine infusion towards a steady-state plasma concentration (arbitrarily set at 1.0). Data from one study using a one-compartment ketamine model (**A**), seven studies using a two-compartment model (**B**), and nine studies using a three-compartment model (**C**). The green line in panel **C** is the simulation based on the meta-analytical three-compartment model. Panel **D** gives the simulated mean arterial (red) and venous (blue) with their 95% confidence interval.

Simulations

For the simulations, 17 studies reporting mixed-effects models were included, with several studies reporting multiple models. Due to the occurrence of outliers, we refrained from including the study from Zhao et al.[28] in the simulations. The overall median time needed to reach 90% of the steady-state concentration was 6.6 h (interquartile range 5.0-13.0 h; range 3-26 h; coefficient of variation of 64%). Normalized concentration-time profiles are shown in Figure 3. For three-compartment models (n = 18), the median time to steady state was 6.6 h (5.7-12.0 h; 4.6-25.6 h; 64%). For the two-compartment models (n = 8), these values were 8 h (4.1-14 h; 3.8-19.6 h; 53.9%). The one-compartmental model (n = 1) showed a shorter median time to steady state of 3.4 h, probably related to the limited number of samples acquired during this study.[33]

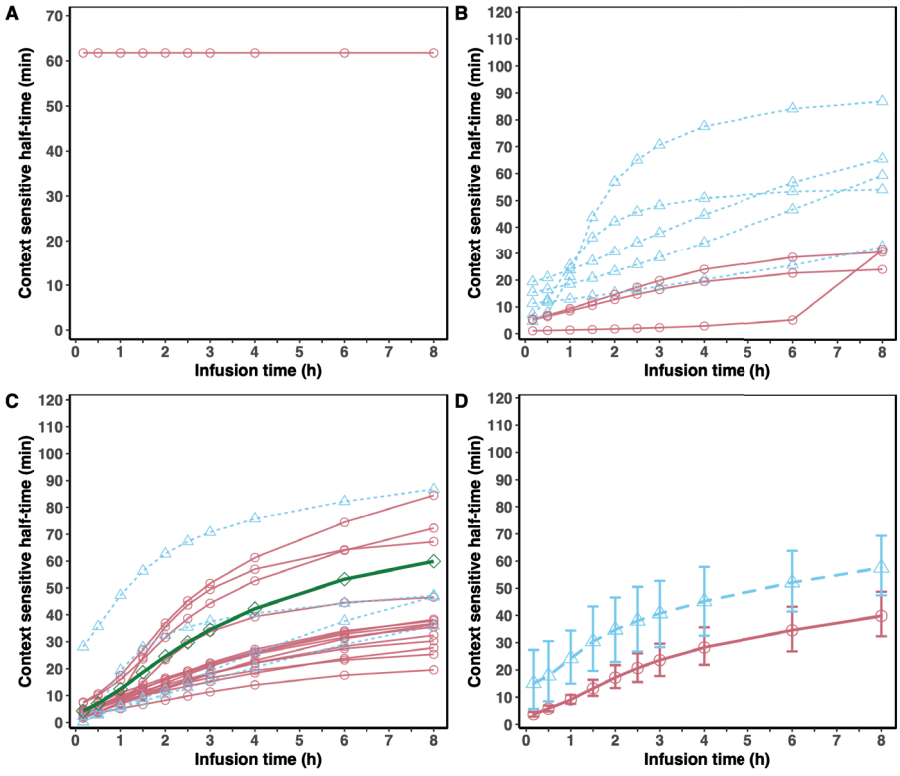

Figure 4. Ketamine context-sensitive half-time curves for each study. Red lines represent models based on arterial samples, blue lines models based on venous samples: (**A**) one-compartment models from one study, (**B**) two-compartment models from seven studies, and (**C**) three-compartment models from nine studies along with the curve (green line) based on the 3-compartmental meta-analytical model. Panel **D** shows the overall mean with the 95% confidence intervals for each evaluation of the arterial *versus* venous models.

No differences were observed in mean concentration-time profiles between arterial and venous sampling (Fig. 3D).

Context-sensitive half-times are shown in Figure 4. Different context-sensitive half-times *versus* infusion time profiles were calculated for one-, two- and three-compartment models separately (panels A-C). As expected, the context-sensitive half-time for the one-compartment model was independent of the infusion time and consequently the decrease in plasma concentration is context-insensitive. In contrast, two- and three-compartment models showed context-sensitive half-time to be dependent on the total infusion duration. On average, the context-sensitive half-time increased to 40 min (arterial sampling) and 55 min (venous sampling) after 8 h of infusion (fig. 4D).

Washout profiles following a 1-min bolus of 0.5 mg/kg ketamine are shown in Figure 5 for a 70 kg individual. Simulations are performed for one-, two- and three-compartment

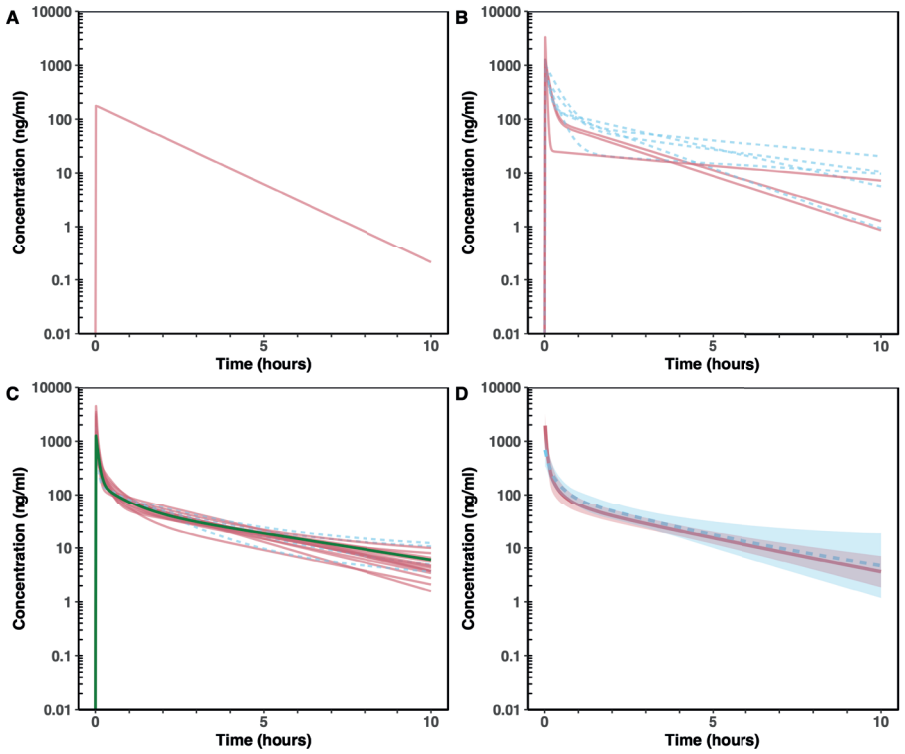

Figure 5. Ketamine wash-in/wash-out profiles of each study following a 1-min bolus infusion of 0.5 mg/kg in a 70 kg individual. Red lines represent models based on arterial samples, blue lines models based on venous samples: (**A**) one-compartment models from one study, (**B**) two-compartment models from seven studies, and (**C**) three-compartment models from nine studies along with the curve (green line) based on the 3-compartmental meta-analytical model. Panel **D** shows the overall mean with the 95% confidence intervals for each evaluation of the arterial *versus* venous models.

models separately (panels A-C) and for models based on venous sampling compared to arterial sampling (Fig. 5D).

Pharmacokinetic population analysis

Raw data sets were obtained from 14 unique sources; included studies are indicated in Table 1. There were two studies (with in total 30 participants) that had two occasions with similar differences in the empirical Bayesian parameters estimates between occasions and subjects. Inter-study variabilities in the pharmacokinetic model parameters were estimated to be small relative to the interindividual variabilities.

However, the inclusion of inter-study variability increased the variability in the final objective function values of the SAEM step, possibly related to the relatively small number of studies. We therefore removed the inter-study variability from the final model.

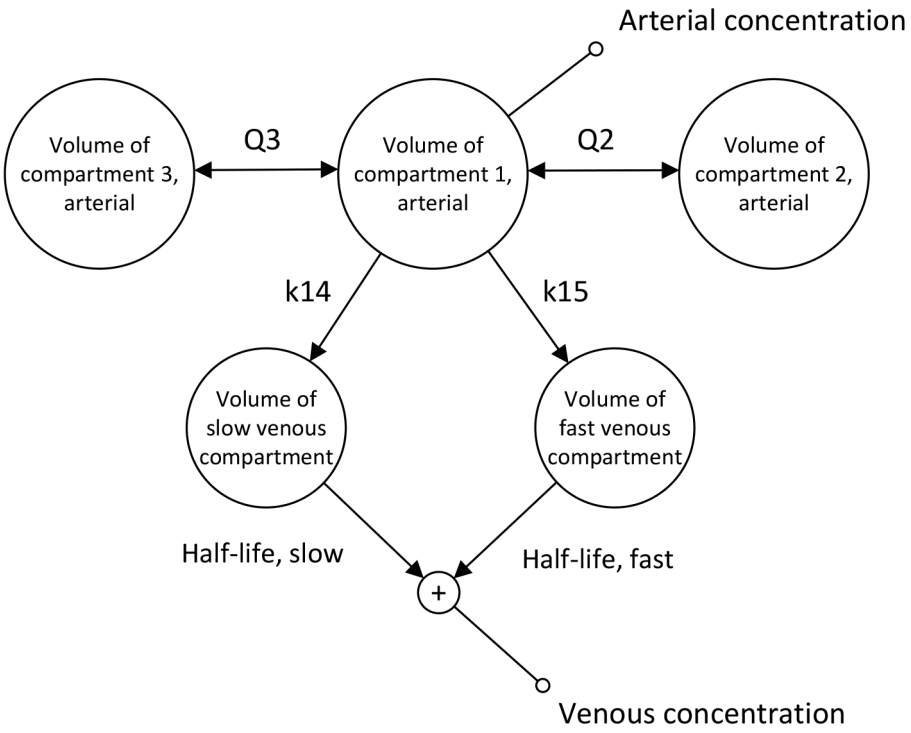

Figure 6. Schematic overview of the raw data model. The arterial concentrations ($C_{arterial}$) were modelled with a three compartmental model (with parameters V1-3$_{artarial}$) with intercompartmental clearances (parameters Q2 and Q3) and an elimination rate constant equal to the sum of parameters k14 and k15. Rate constants k14 and k15 were defined as the arterial elimination rate constant divided by two. To allow for a delay between the arterial and venous plasma concentrations, two venous delay compartments were added ($V_{slow,venous}$ and $V_{fast,venous}$) with elimination half-lives $t_{½,slow}$ and $t_{½,fast}$. Note that k14 = k15 = k10/2 (elimination rate).

The final model consisted of a central compartment with the arterial sampling site and two peripheral body compartments, linked to a fast and a slow venous compartment (Fig. 6). A single peripheral compartment was tested as well but was found significantly inferior to the two peripheral body compartment model ($p < 0.001$). As reported by Henthorn et al.[38] and as shown by the context-sensitive half-time simulations, substantial differences exist between arterial and venous plasma pharmacokinetics. To account for this difference, we added one slow venous delay compartment and one fast venous delay compartment ($V_{ven,slow}$ and $V_{ven,fast}$). The final venous plasma concentration was then defined as: total venous plasma concentration = $C_{ven,fast} * \alpha_1 + C_{ven,slow} * \alpha_2$, in which $C_{ven,slow}$ and $C_{ven,fast}$ the concentrations in the slow and fast venous delay compartments, respectively, and α_1 and α_2 are factors for the contribution of each venous delay compartment to the total venous plasma concentration. For parametrization α_2 was constrained to be $(1 - \alpha_1)$, so that venous concentration lies between two delayed arterial concentrations, where the latter is assumed to be related to diffusion to/from

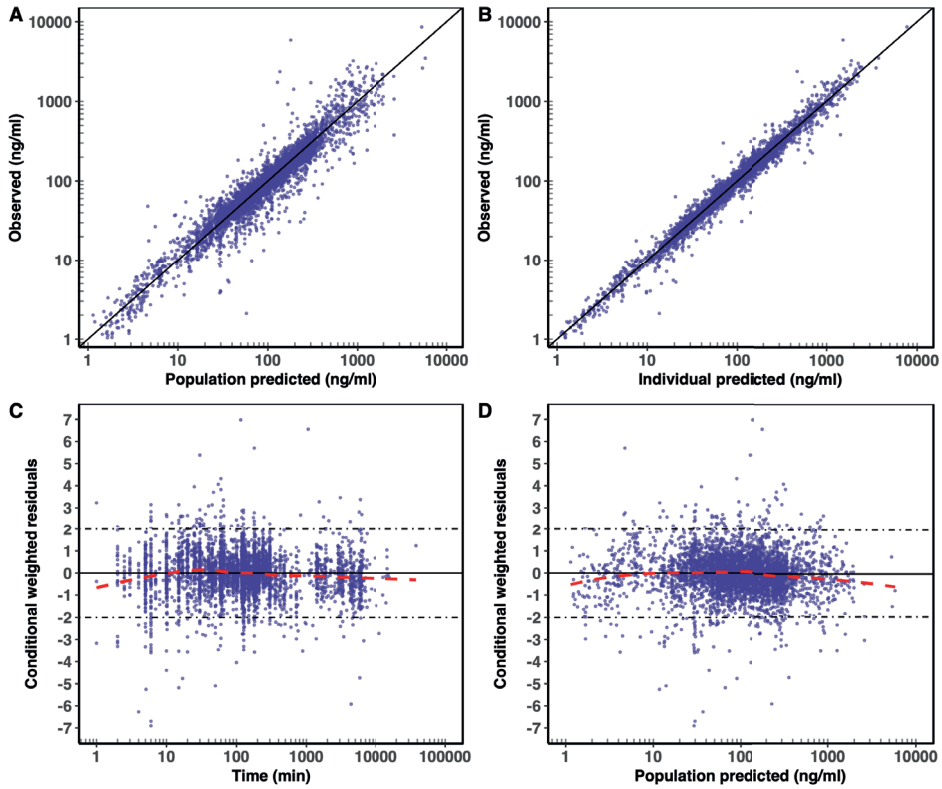

Figure 7. Goodness of fit plots of the raw data model. Observed *versus* population predicted (**A**), observed *versus* individual predicted (**B**), conditional weighted residuals *versus* time (**C**) and conditional weighted residuals *versus* population predicted (**D**).

tissue in the arm. Model parameters are given in Table 3, goodness of fit plots in Figure 7. The goodness of fit plots showed that the model was able to adequately describe the data. In Figure 8, we plotted model parameters against weight to assess whether the use of allometric scaling was adequate. Linear relationships were observed between the parameters and body weight, except for parameter α_1 (Fig. 8I), which indicates that it is reasonable to apply allometric scaling for all parameters except for parameter α_1. Covariate analysis revealed significant effects of analyte on clearance (*R*-ketamine *versus S*-ketamine and *RS*-ketamine *versus S*-ketamine), although the differences are not clinically relevant for short infusion durations, as observed in the simulations (see paragraph below). In Figure 9, we plotted post-hoc η's for clearance against covariates, showing the adequacy of the covariate model.

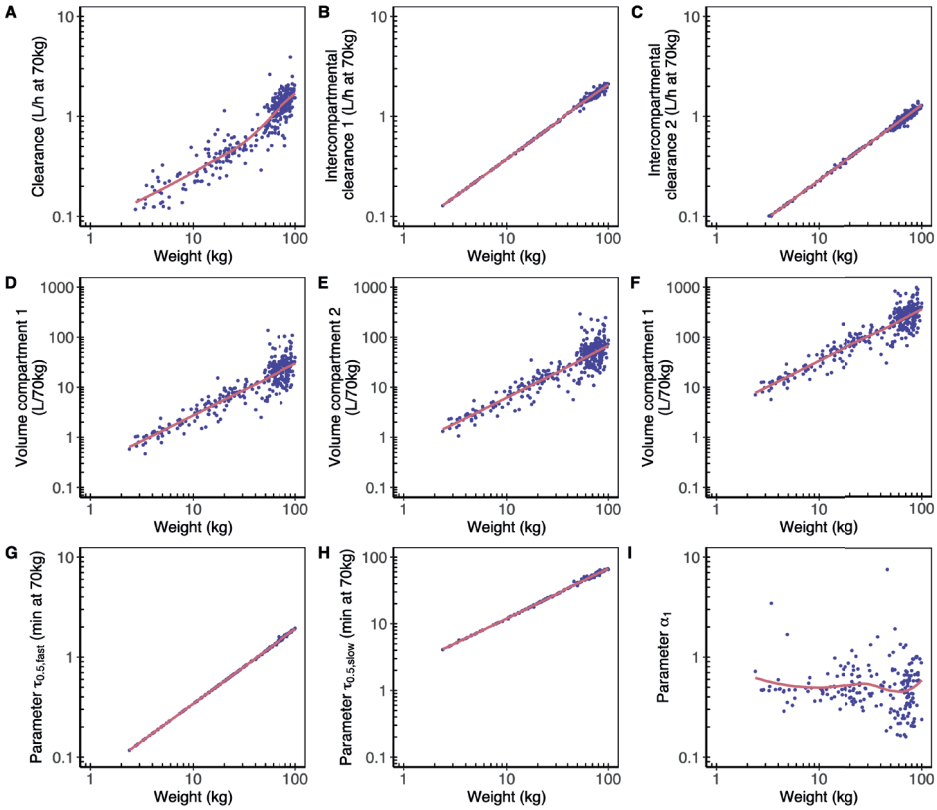

Figure 8. Parameter *versus* subject body weight plots. Clearance, and intercompartmental clearances 1 and 2 against subject body weight (**A-C**); Volume of compartment 1, compartment 2 and compartment 3 against subject body weight (**D-F**); fast and slow elimination half-lives against subject body weight (**G-H**) and Parameter α against subject body weight (**I**). Note that no clear relation is shown between Parameter α and subject body weight.

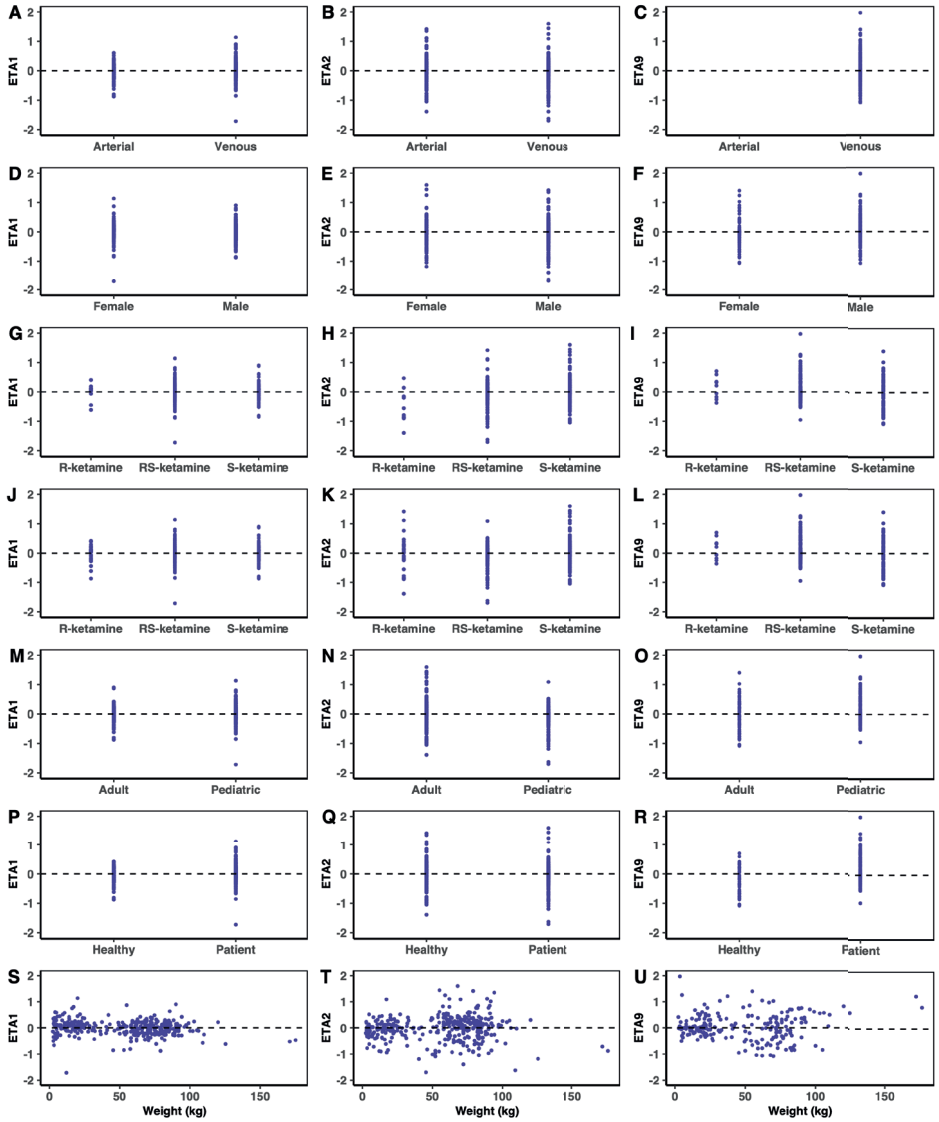

Figure 9. Post hoc ETAs *versus* covariates. Only non-fixed ETA values are shown. ETA1 = inter-individual variabilityfor clearance; ETA2 = inter-individual variability for volume of distribution; ETA9 = inter-individual variability for the $\alpha 1$ parameter. ETAs plotted against arterial versus venous sampling (**A-C**); sex (**D-F**); ketamine administration form (*S*-ketamine, *R*-ketamine, *RS*-ketamine) (**G-I**); measured ketamine enantiomer (*S*-ketamine, *R*-ketamine *RS*-ketamine) (**J-L**); adult *versus* pediatric population (**M-O**); healthy *versus* patient population (**P-R**) and subject body weight (**S-U**). Since parameter α_1 was just applicable for venous sampling, no ETA9 values are plotted for the arterial group (panel **C**).

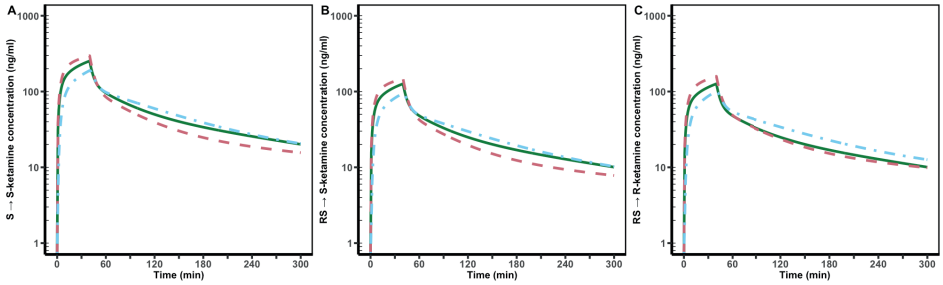

Figure 10. Simulated concentration time profiles with the three-compartment meta-analytical model (green line), and arterial (red line) and venous (blue line) population model derived from the raw data sets after a 40 min infusion of 0.5 mg/kg esketamine or racemic ketamine in a 70 kg person. Three scenarios were simulated: *S*-ketamine concentrations after esketamine administration (**A**), *S*-ketamine after racemic ketamine (**B**) and *R*-ketamine after racemic ketamine (**C**).

Table 3. Pharmacokinetic parameters of the raw data analysis.

	Estimate (% relative standard error)	**% Coefficient of variation (% relative standard error)**
Structural parameters		
Volume of distribution (L/70 kg)	321 (6)	61 (6)
Volume of compartment 1 (L/70 kg)	21 (7)	-
Volume of compartment 2 (L/70 kg)	46 (11)	-
Volume of compartment 3 (L/70 kg)	254 (8)	-
Elimination clearance (L/h at 70 kg)	79 (3)	33 (8)
Intercompartmental clearance 2 (L/h at 70 kg)	97 (5)	-
Intercompartmental clearance 3 (L/h at 70 kg)	60 (7)	-
Parameter $\tau_{0.5,\,fast}$ (min at 70 kg)	1.5 (25)	-
Parameter $\tau_{0.5,\,slow}$ (min at 70 kg)	52 (6)	
Parameter α	0.5 (6)	67 (9)
Covariates		
% decrease in clearance with R-ketamine measured	16 (12)	-
% decrease in clearance with RS-ketamine measured	29 (12)	-

Parameter $\tau_{0.5,slow}$ = elimination half-life slow venous compartment; Parameter $\tau_{0.5,fast}$ = elimination half-life fast venous compartment; Parameter α = scaling factor for the contribution of the fast venous compartment concentrations

The comparison between the raw data model and the three-compartment meta-analytical model are given in Figure 10. These simulations show that the output of the two models are comparable, especially when considering the appreciable uncertainties in the parameter estimates (Tables 2 and 3). Note that since no significant covariate effects were found for the three-compartment meta-analytical model, predictions were the same for this model in all three scenarios. As expected, the three-compartment meta-analytical model predicts higher arterial than venous concentrations during ketamine infusion while the reverse is true during wash-out.

DISCUSSION

We performed an extensive review of literature and retrieved studies that mathematically modelled plasma ketamine concentration data over time. The literature search and selection process resulted in 30 studies with data from a range of populations and settings (healthy volunteers, adult and pediatric patients), with considerable variations in formulations, sample sites, analytes and administration routes. We next performed meta-analyses on studies that performed a mixed-effects analysis. Despite overt heterogeneity, meaningful conclusions were drawn on the quality of studies, statistical approach, pooled weighted ketamine and norketamine model parameter estimates, and ketamine wash-in and wash-out profiles. Additionally, we retrieved 14 raw data sets from the literature and performed a population analysis. Parameter estimates were comparable to the meta-analytical analysis of three-compartment models.

Systematic review

To enable scoring of the quality of the studies, we developed a quality rating system, with focus on data presentation and statistical methods. Several "older" papers scored relatively poorly with score ≤ 4 in studies published before 2007. We included these papers in the systematic review to give a broad overview of all papers on ketamine pharmacokinetic analysis. Moreover, we could not detect an association between the quality score and parameter estimation precision (*i.e.* standard error of the estimates; data not shown). This suggests that while the reporting of data and their analyses may be insufficiently transparent, the underlying parameter estimation process seemed adequate.

Meta-analysis

The values of the ketamine parameter estimates of the 18 studies included in the meta-analysis were well within acceptable margins (within ± 2 times the standard deviation of the population), with the exception of the volume of distribution values extracted

from the study of Zhao et al.[28] In that study, the effect of racemic ketamine in patients with therapy-resistant bipolar depression was evaluated, and separate pharmacokinetic parameter values for *S*- and *R*-ketamine were estimated. They report an *S*-ketamine volume of distribution of 2,187 L/70 kg (about tenfold higher than the overall population value) and a value for *R*-ketamine of 521 L/70 kg. The high body mass index may partly explain the rather large volume of distribution estimates. Ketamine is a lipophilic drug that readily distributes into adipose tissue.[39] Distribution rate constants from the central compartment to compartments two and three were relatively high (k_{12} = 12 h^{-1}, k_{13} = 63 h^{-1}) compared to the redistribution rate constants to the central compartment (k_{21} = 0.04 h^{-1}, k_{31} = 3 h^{-1}). However, this does not explain the difference in parameter estimates between *S*- and *R*-ketamine.

Since in most studies it was assumed that the central ketamine and norketamine volumes of distribution were equal because of identifiability issues, no conclusions can be drawn on potential differences between the norketamine distribution volumes and its parent compound. Moreover, this approach may have increased the variability of all norketamine parameters, because of the varying number of compartments used for the ketamine and/or norketamine data, resulting in different sizes of the volume of compartment 1. The overall population norketamine elimination clearance was about 39% lower than the ketamine clearance (48 *versus* 79 L/h at 70 kg).

Meta-regression did not reveal an influence of covariates on the ketamine and norketamine parameter values. We cannot exclude, however, an approximately 35% difference in clearance between *S*-ketamine following *S*-ketamine administration and *R*-ketamine following racemic ketamine administration in the subpopulation healthy adults. Three studies found a difference between *S*- and *R*-ketamine clearance. Differences in clearance may be related to stereospecific metabolism or to competition for metabolic enzymes.[17,26,38] We observed no differences in ketamine clearance between pediatric and adult populations when adjusted for allometric scaling. Although sometimes stated that ketamine clearance is higher in children,[1] these data are derived from studies following rectal ketamine administration using slow-release suppositories.[40]

Arterial versus venous data

Our dataset includes data from models based on venous and arterial sampling. As shown in the simulation (Fig. 3), concentration-time profiles for venous and arterial sampling models are similar following ketamine infusion towards a steady-state plasma concentration. Importantly, venous sampling was associated with greater context-sensitive half-times for all simulated infusion durations compared to arterial sampling (Fig. 4). Similar findings were reported by Henthorn et al.[38] who showed systematically higher post-infusion concentrations in venous ketamine samples *versus* arterial ketamine samples during simultaneous venous and arterial sampling. The difference in context-

sensitive half-time between arterial and venous data is best explained by the immediate, post-infusion exclusion of partially mixed arterial ketamine concentrations.

Limitations of the meta-analytical approach

Due to their heterogeneity, averaging across studies may have yielded biased parameter values. The heterogeneity is related to differences in study design (such as differences in number of subjects, sampling duration or frequency), differences in assay limits of quantitation and assay quality, and differences in pharmacokinetic model analyses (such as absence of systematic covariance analyses in some studies, two-stage analysis *versus* mixed-effects analysis). In order to limit the degree of heterogeneity, we restricted our meta-analytical approach to studies that applied a mixed-effects analysis and only included three-compartment models in the three-compartment meta-analytical model. Additionally, not only parameters were weighted based on their standard errors, but all studies carried a specific weight in the analysis depending on their methodological quality as determined in the systematic review. Consequently, studies that had methodological issues (all of them were older studies, see Fig. 2) were less influential in the meta-analysis. Variability among studies was therefore significantly reduced with limited influence of single studies in the meta-analytical approach as determined by the sensitivity analysis. Still, in contrast to population analyses of raw data, a meta-analysis is unable to detect within- and between-subject and between-study variability. In summary, we do acknowledge the limitations of the meta-analytical approach but given ourselection process and quality-weighted analysis, we argue that the parameter estimates derived from our meta-analytical approach had acceptable bias (see paragraph below on the differences in pooled parameter values and parameter estimates of the population analysis).

Population analysis versus meta-analysis

We were able to construct a stable population model from 14 raw data sets that we partly retrieved from our collaborators. Studies included were pediatric and adult data sets and studies measuring venous and/or arterial concentrations. In the 5-compartment population model, the transition from arterial to venous compartments was best described by fast and slow transition pathways (elimination half-times 1.5 min *versus* 52 min), which is related to the differences in arterial and venous plasma pharmacokinetics.[38] The number of included studies in the population analysis was 20% less than the number of studies included in the meta-analysis, which may account for the difference in the value of the estimated volumes of distribution between analyses (252 L/70kg *versus* 321 L/70kg for the meta-analysis and population analysis, respectively); in contrast, clearances were very similar (79 L/h at 70 kg *versus* 79 L/h at 70 kg for the meta-analysis and population analysis, respectively). Additionally, in contrast to the

meta-analytical approach, a significant covariate (analyte) was detected. Despite these differences, simulations show that differences in the plasma concentration profiles are comparable between the two approaches, during and following short-term ketamine infusion (Fig. 9). Although this seems reassuring and suggests that the meta-analytical approach is an adequate approximation of the population analysis in NONMEM, pharmacokinetic meta-analyses should be restricted to conditions in which raw data are unavailable. With nonlinear mixed-effects modeling, the best separation of sources of variability is possible (between- and within-subject variability and between-study variability), in principle, but in our case was hampered by the heterogeneity and relatively low number of studies (n = 14); in the meta-analytical approach it is unclear how to obtain estimates of the magnitudes of these variabilities. Further studies, studying long-term ketamine infusion and incorporating ketamine metabolites and possibly other inputs such as metabolic enzyme genotype in the model, are necessary to further compare the two methods and their reliability in obtaining better parameter estimates in the heterogeneous clinical population.

CONCLUSIONS

We present three distinct analyses, that summarize and compare ketamine pharmacokinetic parameters from different studies and populations. First, in the meta-analytical approach, we estimated model parameters, volume of distribution and clearance, and did not observe large differences between healthy volunteers and patients, pediatric or adult. Next, we calculated meta-analytical model parameters for a three-compartment pharmacokinetic model. Finally, we performed a population pharmacokinetic analysis of 14 raw data sets and were able to construct a reliable model that allowed prediction of arterial and venous ketamine concentrations without clinically significant involvement of covariates. Simulations showed that the output of the meta-analytical and raw data models were comparable. We suggest that the meta-analytical pharmacokinetic model and population pharmacokinetic analyses of multiple raw datasets yield roughly equivalent parameter estimates for use of ketamine in clinical settings. Still, since the population analysis of raw data is superior, we advise to limit the pharmacokinetic meta-analyses to conditions in which no or just limited raw data sets are available.

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SUPPLEMENTAL DATA: KETAMINE PHARMACOKINETIC STUDY GROUP MEMBERS

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4

Pharmacokinetics of ketamine and its major metabolites norketamine, hydroxynorketamine and dehydronorketamine: a model-based analysis

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Ketamine, first synthetized in the early 1960s, is currently experiencing a renewed interest with applications in a variety of indications. It was initially developed as dissociative anesthetic and as a safer alternative to phencyclidine, causing less excitation upon emergence from anesthesia.[1] Presently, ketamine is increasingly used for treatment of acute (perioperative) pain, chronic neuropathic pain and therapy-resistant clinical depression. [1,2] While ketamine interacts with multiple receptor systems, its blockade of the *N*-methyl-D-aspartate receptor (NMDAR) is considered pivotal in producing anesthesia, pain relief and anti-depressant effects. [1,3] Ketamine is a racemic mixture (*RS*-ketamine) and is available in two commercial formulations. The racemic mixture (Ketalar) has been around for many years and is used in human and veterinary medicine. More recently (since 1997) the *S*-enantiomer (Ketanest) has been marketed in various European countries for the same indications as *RS*-ketamine, while in 2019 esketamine for intranasal administration (Spravato™) was registered in the United States and the European Union for treatment of therapy-resistant depression.[4-6] There are substantial differences in potency between the *S*- and *R*-ketamine isomers. For example, *S*-ketamine has a twofold greater anesthetic potency relative to the racemic,[7] the *R*-variant is three times more potent in its antidepressant effects than *S*-ketamine.[5]

Ketamine is extensively metabolized by cytochrome P450 enzymes, particularly by CYP2B6 and CYP3A4.[6,8] The main metabolic pathway involves demethylation to norketamine which is subsequently metabolized to dehydronorketamine (DHNK) and hydroxynorketamine (HNK).[1,9] These secondary metabolites, DHNK and HNK, were for a long time considered inactive or clinically irrelevant. However, recent studies showed activity of HNK in producing analgesia and antidepression.[5,10,11] Little is known about the pharmacokinetic behavior of these metabolites in humans. We found just one study, performed in nine patients with bipolar depression, that included DHNK and HNK in a pharmacokinetic analysis.[12] In the current study, we performed a population pharmacokinetic modeling study of ketamine and its metabolites (norketamine, DHNK end HNK) following administration of escalating doses of the racemic mixture and *S*-ketamine in twenty healthy volunteers. In this study both drugs were administered without and with a continuous infusion of the nitric oxide donor sodium nitroprusside (SNP). SNP was used to assess its ability to tame the schizotypal side effects of ketamine. The descriptive results of this study have been published before.[13] The main aim of this secondary analysis was to develop a mixed-effects population pharmacokinetic model for ketamine and its most important metabolites.

METHODS

Ethics and subjects

The current study is part of a large project on the efficacy of SNP in reducing the central and peripheral adverse effects of *RS*- and *S*-ketamine (*e.g.* drug high, schizotypal symptoms, and increased cardiac output). Secondary analyses were planned: (1) development of a population pharmacokinetic model of *RS*- and *S*-ketamine and their metabolites; (2) pharmacokinetic-pharmacodynamic modeling of the analgesic and psychotomimetic effects of *RS*- and *S*-ketamine ketamine; (3) pharmacokinetic-pharmacodynamic modeling of the effects of *RS*-and *S*-ketamine on cardiac output. Here we report on item (1). The study protocol was approved by the institutional review board of the Leiden University Medical Centre (CME, Leiden, the Netherlands) and the Central Committee on Research involving Human subjects (CCMO, The Hague, The Netherlands). The study was registered at the trial register of the Dutch Cochrane Center (www.trialregister.nl) under identifier 5359. All procedures were performed in compliance with the latest version of the Declaration of Helsinki and Good Clinical Practice guidelines.

Subject enrollment was performed as previously published.[13] In brief, healthy male subjects, aged 18-34 year and with a maximum body mass index of 30 kg m^{-2}, were recruited. For a complete list of exclusion criteria see Ref. 12. Importantly, subjects were excluded when they used any medication or herbs/vitamins in the 3 months before dosing. Additionally, they were not allowed to consume any caffeinated food or beverages in the 24 h before dosing or consume any grapefruit-containing food or beverages in the 7 days before dosing. No consumption of any food or drinks were allowed for 8 hours before dosing.

Study design

Drugs

The study had a double-blind, crossover and randomized design. All subjects were studied on 4 occasions, which were identical in their design, except for the drug combinations that were administered. On visits A and B, participants received escalating doses of intravenous *RS*-ketamine (Ketalar, Pfizer Pharma, Berlin, Germany), on visits C and D, they received escalating doses of *S*-ketamine (Ketananest-S, Eurocept BV, Ankeveen, the Netherlands). Additionally, subjects received intravenous placebo on visits A and C, and intravenous SNP (0.5 mg kg^{-1} min^{-1}) on visits B and D (the sequence of visits was randomized). Ketamine and SNP were infused via two distinct intravenous access lines placed on the ipsilateral hand and arm. *RS*-ketamine was administered according to the following infusion scheme: 0-60 min: 0.28 mg kg^{-1} h^{-1}, 60-120 min: 0.57 mg kg^{-1} h^{-1} and 120-180 min: 1.14 mg kg^{-1} h^{-1}; the equivalent *S*-ketamine infusion scheme was: 0-60 min: 0.14 mg kg^{-1} h^{-1}, 60-120 min: 0.28 mg kg^{-1} h^{-1} and 120- 180 min: 0.57 mg

kg^{-1} h^{-1}. The difference in dosing was based on observations that *S*-ketamine has twice the potency compared to *RS*-ketamine as based on a pilot study, in which psychedelic symptoms were evaluated after a 50 mg dose of both drugs.

Randomization and blinding

The sequence of the study visits was randomized using a computer-generated randomization list with a four-block design (www.randomization.org). The pharmacy was informed on the day prior to the study visit of the subject weight, subject and visit codes (#A-D). The pharmacy prepared the medication on the morning of the study visit according to Good Manufacturing Practice guidelines and the randomization list. Two syringes containing ketamine (*RS*-/*S*-ketamine) and placebo/SNP were dispensed to the research team in 50 mL syringes marked with the numerical subject and visit code and treatment (ketamine or SNP), ensuring full blinding of the research team. The research team remained blinded until all data were collected.

Blood sampling and analysis

Eight mL arterial blood samples were obtained on each occasion at predefined sampling times: t = 0 (baseline), and 2, 6, 30, 59, 62, 66, 100, 119, 122, 126, 150, 179, 182, 186, 195, 210 and 300 min after the start of ketamine infusion. Samples were drawn from an arterial line, which was placed in the radial artery of the arm opposite to the arm where the intravenous line was placed for drug infusion.

Plasma samples were analyzed in the laboratory of dr. Evan Kharasch (Washington University School of Medicine, St. Louis, MO) as extensively described by Rao et al.[13] An enantioselective assay was used for ketamine, norketamine and DHNK analyses. For HNK, total *S*- and *R*-concentrations were determined. For ketamine, norketamine and DHNK, the lower and upper limits of quantitation were 2.5 and 250 ng mL^{-1} and for HNK 5 and 500 ng mL^{-1}.

Population pharmacokinetic analysis

Model development

To account for the differences in molecular weight between ketamine and the metabolites, concentration data were converted from ng mL^{-1} to nmol mL^{-1}. Data analysis was performed in a stepwise fashion. First, the stereoselective ketamine data were analyzed using a three-compartment model, similar to the published model by Sigtermans et al.[14] Additionally, one and two compartment models were evaluated. Next, the best ketamine model was expanded by one to four metabolic delay compartments to model norketamine formation. Since no norketamine was administered, the volume of the central norketamine compartment (V_1) was not identifiable. It was therefore assumed that the volumes of the central ketamine and norketamine compartments were equal.

Since the kinetics of the central norketamine compartment could not be estimated from the data, we assumed that the amount of drug in the norketamine central compartment was in steady state (equilibrium) with respect to its peripheral and metabolism compartments.[14] Consequently, since the norketamine formation and elimination rates are then not both identifiable, the norketamine formation rate and ketamine elimination rate were assumed equal.[9,12,14] Different norketamine models with one, two or three norketamine compartments were fitted to the data. Finally, the optimal norketamine model was expanded with one to three metabolic compartments to model HNK and DHNK formation. Similar to norketamine, the volumes of DHNK and HNK V_1 were not identifiable and therefore set equal to the volume of ketamine V_1 and the sum of the DHNK and HNK formation rates was set equal to the norketamine elimination rate. Since no stereospecific HNK data were available, HNK formation was modeled as the sum from the separate *S*- and *R*-ketamine pathways.

To standardize the pharmacokinetic model parameters, and to add body weight (WT) information to the model, clearances were allometrically scaled to liters per hour at 70 kg by $CL = (WT/70)^{0.75}$. Furthermore, compartment volumes were scaled to 70 kg body weight by V = WT/70. Model selection was based on a significant decrease in objective function value (OFV) calculated as -2LogLikelihood (χ^2-test, with $p < 0.01$ considered significant) and by assessing the goodness of fit by visual inspection of data fits, and goodness of fit plots: normalized prediction distribution error *versus* time plots, normalized prediction distribution error *versus* predicted plots and predicted *versus* measured plots. Moreover, prediction-variance-corrected visual prediction checks (VPCs) were performed by simulating 1000 datasets based on the model parameters and comparing the simulated quantiles with those of the true data.

Statistical analysis

The data were analyzed in NONMEM version 7.4.3 (ICON Development Solutions, Hanover, Maryland). The M3 method for data censoring, as published by Beal et al., was used for data below the level of quantitation and data above the upper limit of the calibration curve.[15] The LAPLACE-I estimation algorithm was used to estimate model parameters. To account for interindividual and inter-occasion variability (IOV), random effects were included in the model with an exponential relation: $\theta_i = \theta \times \exp(\eta_i + \eta_{iov})$, where θ_i is the parameter for individual i, θ the population parameter, η_i is the random difference between the population and individual parameter and η_{iov} the difference between θ_i and θ due to inter-occasion variability. In addition, proportional and additive errors were evaluated for each separate analyte to account for residual variability. The proportional and combined proportional and additive error models were described by: $Y_{ij} = F_{ij} \times (1 + \varepsilon_{ij})$ and $Y_{ij} = F_{ij} \times (1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$ respectively, where Y_{ij} is the j^{th} observed plasma concentration for individual i, F_{ij} is the corresponding model-prediction, and $_{ij}$ is

the residual error. The standard errors of the estimates (SEE) were based on NONMEM's covariance step without specifying a MATRIX option, so the default was used (i.e., the "Sandwich" matrix).

To test the effects of potential covariates the model, we performed a covariate search using an automated stepwise covariate screening algorithm (Stepwise Covariate Model building module from PsN).[16] Characteristics included in the covariate testing were: (i) analyte enantiomer (*S*- or *R*-isomer), (ii) placebo or SNP administration, and (iii) *S*-ketamine or *RS*-ketamine infused. Covariates were first tested by a forward search algorithm that sequentially added covariates that caused a significant drop in objective function value (OFV, $p < 0.01$) to the model. The relation between a covariate and a pharmacokinetic parameter was modeled as a linear relation with the formula: $\theta_i = \theta_{ref} \times (1 + \theta_{COV})$, where θ_{ref} is the typical parameter value for a subject with the reference category of the covariate and θ_{COV} the effect of belonging to the non-reference category. The covariate causing the largest decrease in OFV was included in the first step of the forward search, followed by the covariate causing the second largest decrease. This process continued until either no covariates were left for inclusion or when the remaining covariates were unable to cause a significant decrease in OFV. The final forward model was used for the backward selection, in which a similar strategy was used, although now covariates were removed from the model. Removed covariates that did not cause a significant worsening of the OFV ($p < 0.001$) were permanently excluded from the model. Covariates were maintained in the model when their removal caused a significant worsening of the OFV. This process continued until all covariates were excluded or until the covariates remaining in the model caused a significant worsening in OFV when removed.

Simulations

The clinical relevance of the covariates that were added to the model by Stepwise Covariate Model building, was evaluated by in simulation studies. The ketamine, norketamine, DHNK and HNK concentration time relationships of dose escalating ketamine infusions were simulated for a 70 kg individual and were performed using the RxODE package (version 0.8.0-9) for R studio (version 1.1.456, 2009-2018 RStudio, Inc). Three different conditions were simulated: *S*-ketamine after *S*-ketamine infusion, *S*-ketamine after *RS*-ketamine infusion and *R*-ketamine after *RS*-ketamine infusion. Furthermore, the effect size of SNP was evaluated by simulating each of these conditions without and with infusions of SNP. To evaluate ketamine and metabolite concentrations in a clinical scenario, plasma concentrations were simulated for a typical 70 kg individual, following a dose of 0.5 mg/kg *S*-ketamine or *RS*-ketamine infused in 40 minutes.

RESULTS

All 20 subjects completed the four visits without serious adverse events. Mean ± SD (range) subject body weight was 83 ± 9 (60-98) kg, height 186 ± 6 (175-193) cm, age 23 ± 2 (19-28) years and body mass index 24.0 ± 2.1 (19.5-28.4) kg m^{-2}. Complete concentration curves were obtained in all subjects, with the exception for one visit of one subject due to the inability to place the arterial line. A complete overview of the subject selection is shown in the consort flowchart (Supplemental figure 1). Ketamine, norketamine, DHNK and HNK concentrations are shown in Figure 1.

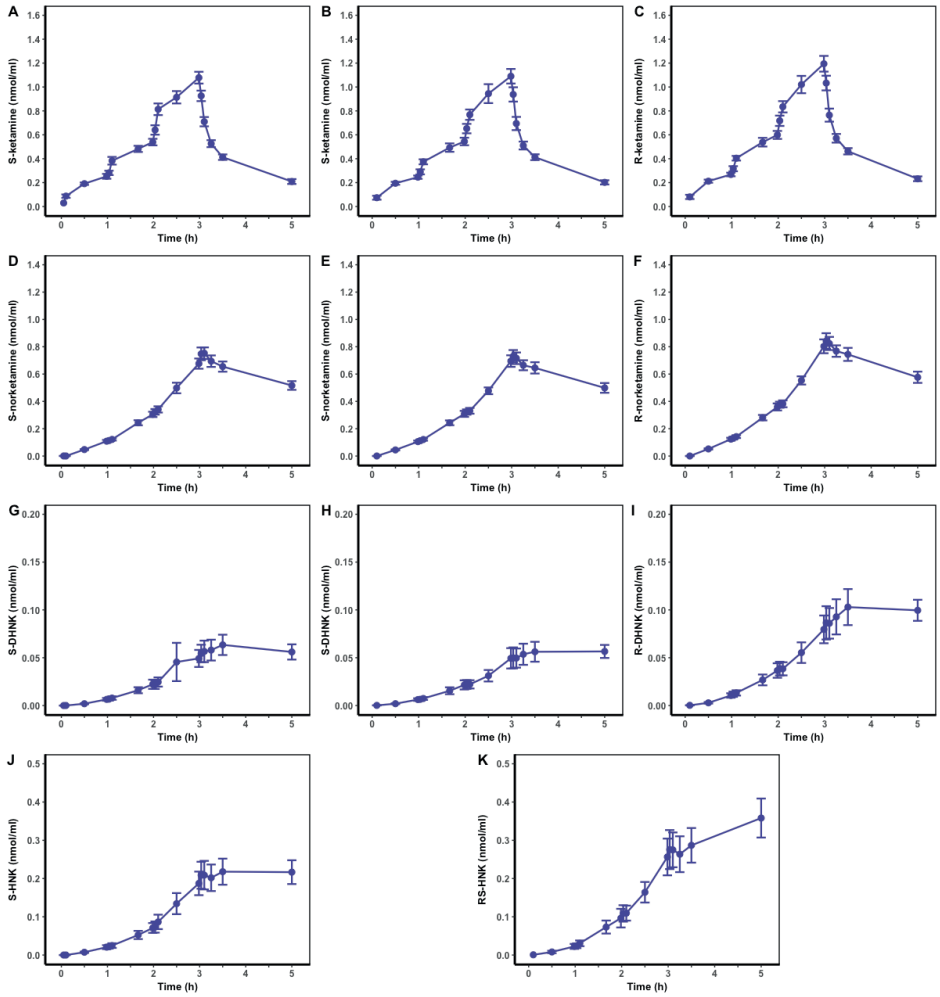

Figure 1. Mean plasma concentrations (+/- SE) of *S*-ketamine, *S*-norketamine and *S*-DHNK after esketamine (**A,D,G**); *S*-ketamine, *S*-norketamine and *S*-DHNK after racemic (**B,E,H**); *R*-ketamine, *R*-norketamine and *R*-DHNK after racemic ketamine administration (**C,F,I**) and total HNK plasma concentrations after racemic ketamine (**I**).

Peak concentrations

An overview of peak concentrations (C_{MAX}) with their respective times (T_{MAX}) are shown in Supplemental Table 1. Following racemic ketamine infusion, higher peak *R*- than *S*-enantiomer plasma concentrations were observed for ketamine, norketamine and DHNK. Importantly, the concentration difference between the enantiomers increased with each metabolic step (*i.e,* the enantiomer concentration difference was greater for DHNK than for norketamine). Metabolite peak concentrations were delayed relative to the ketamine peak concentrations (ketamine T_{MAX} = 170-173 min) by 17 min for norketamine (irrespective of formulation) and 80-120 min for DHNK; the delay in HNK peak concentration was 81 min following *S*-ketamine infusion and 69-72 min following racemic ketamine. Note however, that not all subjects reached their HNK and DHNK C_{MAX} within the sampling time (Fig. 1). For ketamine, 12% of measured plasma concentrations (n = 241) were below or above the lower and upper level of quantitation, for norketamine 6.6% (n = 127), for DHNK 30% (n = 580) and for HNK 14% (n = 149).

Structural pharmacokinetic model

The final model structure is shown in Figure 2. Ketamine pharmacokinetics were best described by a two-compartment model (ΔOFV = -6976). Adding significant covariates resulted in a further improvement of the ketamine model to an ΔOFV of -7130 points (Table 1). Norketamine was best modelled with two norketamine disposition compartments (ΔOFV = -8635). Extending the model by adding two metabolic delay compartments for the norketamine formation, improved the model by 70 points. The model was further improved by 702 points after addition of covariates. It was not possible to estimate the separate norketamine fractions that were metabolized to DHNK and HNK. We considered three different conditions with different fixed fractions for the DHNK and HNK formation 30%:70%, 40%:60% and 50%:50% (DHNK%:HNK%) from norketamine to overcome structural parameter un-identifiability.

Based on the observed plasma concentrations (Fig. 1 and Supplemental Table 1), we assumed that the fraction 30%:70% was most realistic, and present the data analysis using this conversion rate. DHNK was best modeled with one metabolic delay compartment and one disposition compartment (ΔOFV = -9212). The covariates caused a further OFV drop of 2349 points. In contrast, one HNK metabolic compartment coupled to one HNK disposition compartment showed a clear discrepancy in the elimination phase in the VPC. A model with two disposition compartments without a metabolic compartment solved this problem (ΔOFV = -5106). Adding covariates further improved the model by 26 points.

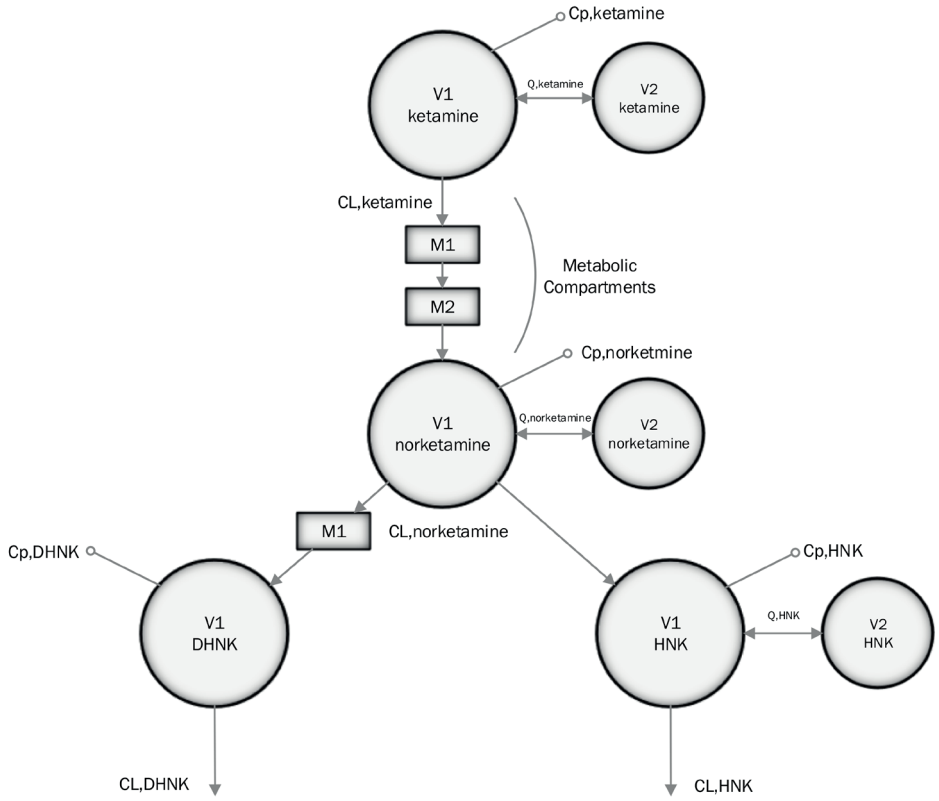

Figure 2. Schematic overview of the final pharmacokinetic model for ketamine, norketamine, DHNK and HNK. V1,ketamine; V2,ketamine; CL,ketamine and Q,ketamine represent the central and peripheral ketamine compartments and the ketamine elimination and intercompartmental clearances respectively. Norketamine formation is modelled via 2 metabolic compartments (M1-2). V1,norketamine; V2,norketamine; CL,norketamine and Q,norketamine represent the central and peripheral norketamine compartments and norketamine elimination and intercompartmental clearances respectively. DHNK formation from norketamine was modeled via one metabolic compartment (M1). DHNK was modeled with one disposition compartment (V1,DHNK) with elimination clearance CL, DHNK. No metabolic compartments were used for the formation of HNK from norketamine. V1, HNK and V2,HNK represent the central and peripheral HNK compartments respectively with elimination clearance CL, HNK and intercompartmental clearance Q,HNK.

Pharmacokinetic model parameters

To get an indication of the, best, median and worst fits based on the coefficient of determination (R^2), model fits are given in Figure 3 for pooled ketamine (Fig. 3A-C), norketamine (Fig. 3D-F), DHNK (Fig. 3G-I) and HNK (Fig. 3J-L) data sets. Goodness of fit plots are given in Supplemental Figure 2, showing a small misfit for *R*- and *S*-ketamine (panels A and B); the model slightly overestimates ketamine plasma concentrations at the lower concentration ranges. Otherwise, data fits and goodness of fit plots indicate that the

Table 1. Population pharmacokinetic model parameters

	Parameter estimates		
	Typical parameter value ± SEE (%CV)	**Inter-individual variability ± SEE (%CV)**	**Inter-occasion variability ± SEE (%CV)**
Ketamine			
V_1 (L/70 kg)	25.8 ± 1.5 (6)	20.2 ± 4.85% (24)	20 ± 2.60% (13)
V_2 (L/70 kg)	115 ± 5.8 (5)	17.6 ± 2.82% (16)	-
CL (L/h at 70 kg)	106.8 ± 3.2 (3)	10.7 ± 1.5% (14)	10.3 ± 0.93% (9)
Q (L/h at 70 kg)	126 ± 6.3 (5)	20.5 ± 5.13% (25)	-
additive error (nmol/L)	38.9 ± 2.3 (6)	-	-
proportional error	0.108 ± 0.006 (6)	-	-
Covariates			
CL (% decrease when R-ket)	11.5 ± 0.58 (5)	-	-
CL (% increase when SNP)	9.2 ± 2.22 (24)	-	-
Q (% increase when SNP)	21.6 ± 5.18 (24)	-	-
Norketamine			
V_2 (L/70 kg)	240 ± 19.2 (8)	25.2 ± 4.28% (17)	36 ± 3.24% (9)
CL (L/h at 70 kg)	59.9 ± 3.6 (6)	-	-
Q (L/h at 70 kg)	196.2 ± 9.8 (5)	19.7 ± 3.35% (17)	24.2 ± 2.42% (10)
MTT (min)	26.6 ± 2.1 (3)	-	-
additive error (nmol/L)	-	-	-
proportional error	0.12 ± 0.005 (4)	-	-
Covariates			
CL (% decrease when R-norketamine)	26.9 ± 2.15 (8)	-	-
Q (% decrease when R-norketamine)	22.1 ± 2.43 (11)	-	-
Dehydronorketamine			
CL (L/h at 70 kg)	185.4 ± 20.39 (11)	44.1 ± 7.5% (17)	21.2 ± 2.12% (10)
MTT (min)	36.9 ± 2.95 (8)	36.9 ± 29.52% (8)	-
additive error (nmol/L)	1.82 ± 0.25 (14)	-	-
proportional error	0.141 ± 0.01 (7)	-	-
Covariates			
CL (% decrease when R-DHNK)	49.3 ± 3.94 (8)	-	-
MTT (% increase when racemic ketamine)	20 ± 12.2 (61)		
MTT (% decrease when R-DHNK)	16.1 ± 13.36 (83)		
Hydroxynorketamine			
V_2 (L/70 kg)	216 ± 41 (19)	-	-
CL (L/h at 70 kg)	76.2 ± 20.60 (27)	86 ± 21.5% (25)	62.4 ± 7.49% (12)
Q (L/h at 70 kg)	218.4 ± 45.90 (21)	64.4 ± 23.18% (36)	34.6 ± 6.23% (18)
additive error (nmol/L)	5.88 ± 1.2 (20)	-	-
proportional error	0.249 ± 0.01 (8)	-	-
Covariates			
Q (% increase when Racemic)	114 ± 39.9	-	-

SEE = standard error of the estimate; %CV = % coefficient of variation, calculated as the SEE / typical parameter value * 100; V_1 = volume central compartment; V_2 = volume peripheral compartment, CL = elimination clearance, Q = intercompartmental clearance, MTT = mean transition time. Central compartment volumes (V_1) for NKT, DHNK and HNK were assumed to be equal to that of KET.

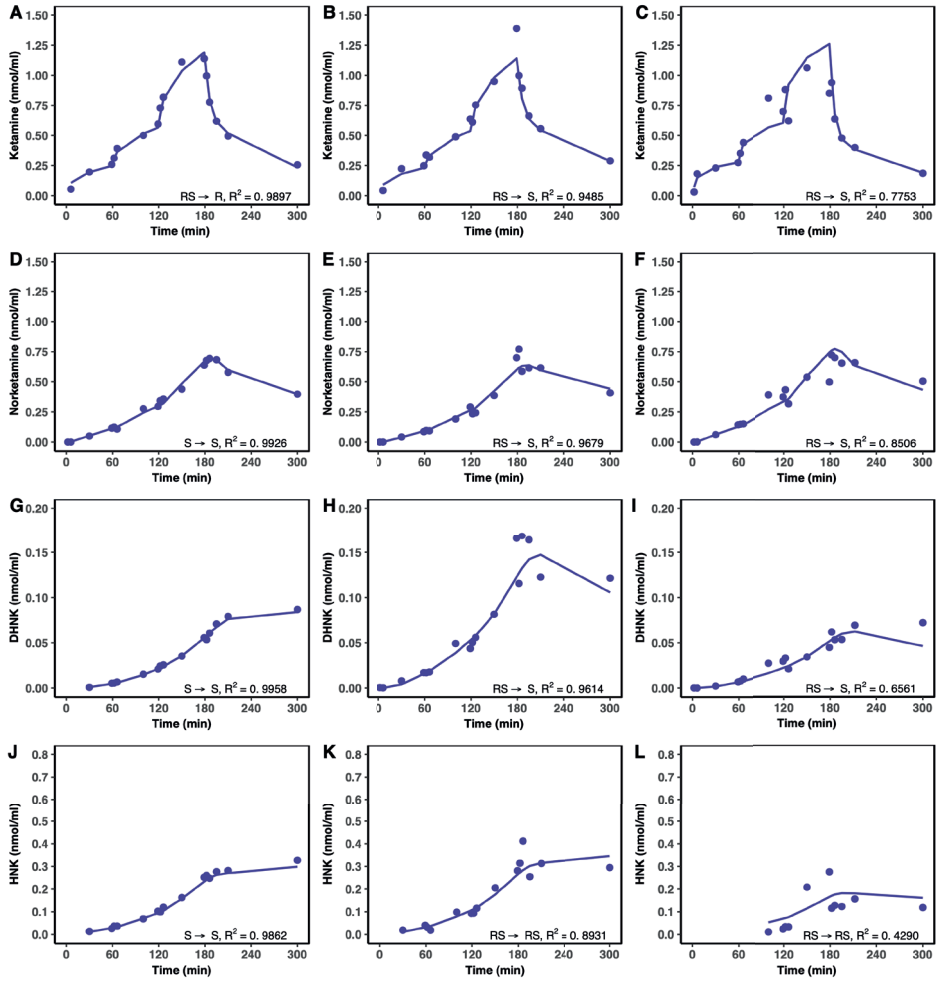

Figure 3. Pharmacokinetic model fits. Best (left panels), median (center panels) and worst (right panels) fits for pooled ketamine (**A-C**), norketamine (**D-F**), DHNK (**G-I**) and HNK (**J-L**) data sets. The circles represent the true data. The lines are the model fits.

model adequately describes the data. The Visual Predictive Checks are given in Supplemental Figures 3-6. No overt misfits became apparent with 95% of measured data points within the 95% prediction intervals for the simulated ketamine, norketamine and HNK data; for DHNK some of the data points at the highest dose (180 min) lie above the 95% prediction interval. The simulated 95% prediction intervals of the proportions of the data under the lower limit of quantitation (LLOQ) or above the upper limit of quantitation (ULOQ) were generally in agreement with the observed proportions. For HNK, a small misfit was observed for the proportion of the data under the LLOQ at the begin of the sampling scheme (Supplemental figure 6B). The observed proportion of

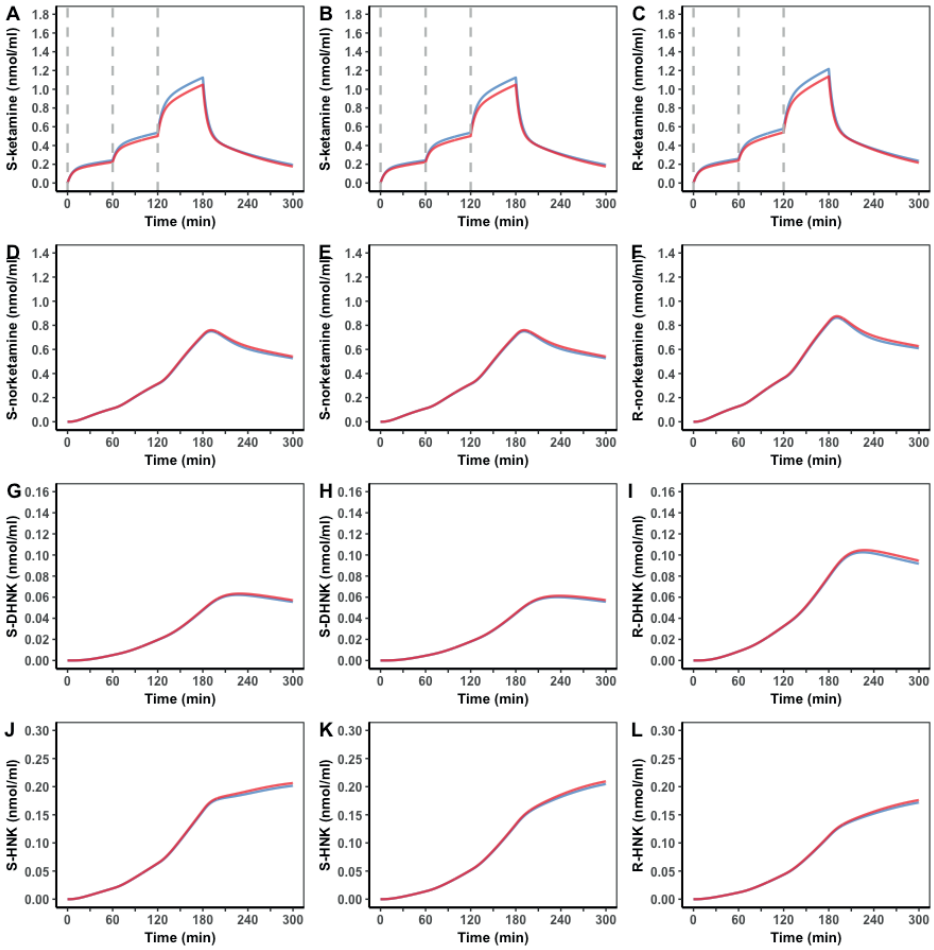

Figure 4. Model simulations. Simulated concentration time profiles for a 70 kg individual after receiving escalating esketamine infusions (left panels) or racemic ketamine (center and right panels) and with concomitant placebo administration (blue lines) or with SNP (red lines). Gray lines indicate the start of each ketamine dose.

0.5 was due to the limited number of samples in which HNK could be detected (n = 2). Of these two samples, one sample was above the LLOQ and one sample was under the LLOQ and could therefore not be reliably quantified.

Parameter estimates and included covariates are given in Table 1. The *R*-enantiomers of ketamine, norketamine and DHNK had a 11.5-49.3% lower elimination clearance than their *S*-variants. For ketamine, concomitant administration of SNP was associated with a 9.2% increase in elimination and a 21.6% increase in intercompartmental clearance. Since HNK plasma levels were not measured stereo-selectively, only the effects of the formulation (racemic- and *S*-ketamine) and concomitant infusion of SNP or placebo

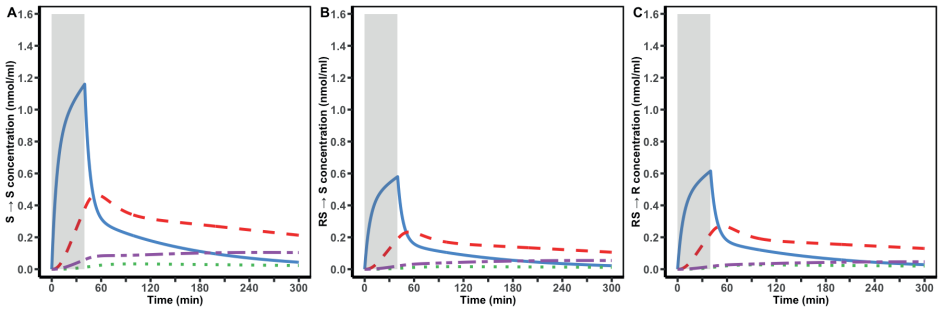

Figure 5. Simulations in clinical context. Concentration time profiles of ketamine, norketamine, DHNK and HNK (blue, red, green and purple lines respectively) after 0.5 mg/kg esketamine (**A**) or racemic ketamine (**B, C**) in a 70 kg individual. Note that, since racemic ketamine consists for 50% out of *S*-ketamine and for 50% out of *R*-ketamine, peak concentrations for *S*-ketamine and *R*-ketamine after racemic ketamine (**B,C**) are approximately half of the *S*-ketamine peak concentration after esketamine. Highlighted area indicates duration of infusion.

could be tested. SNP had no effect on HNK pharmacokinetics. Following *RS*-ketamine infusion the HNK intercompartmental clearance increased by 114% relative to just *S*-ketamine infusion.

Simulations

In addition to the automated covariate search, the exploration of the importance of the included covariates was assessed through simulations. The effect of the two formulations (racemic versus *S*-ketamine) and co-administration of SNP or placebo on plasma concentrations was simulated using the same infusion paradigm as in the experimental study (Fig. 4). Overall, the effects of the covariates were small.

Administration of SNP caused small (< 10%) reductions in peak *S*- and *R*-ketamine concentrations, irrespective of the formulation (red *versus* blue (placebo) lines in Fig. 4A-C), which is explained by the higher ketamine clearances during SNP administration. However, this difference was not seen for the metabolites. The formulation had no effect on the *S*-ketamine plasma concentrations. Peak *R*-ketamine concentration following racemic ketamine infusion was higher than the *S*-ketamine concentrations following racemic or *S*-ketamine infusion. This effect was about 10%, which is due to the lower *R*- than *S*-ketamine clearance. Similarly, peak *R*-norketamine and *R*-DHNK concentrations were higher than the *S*-variant following racemic ketamine infusion by factors 1.2 and 1.7, respectively. Although no stereo-selective data were obtained for HNK, the simulations (that considered *S*-HNK formation following *S*-ketamine infusion; Fig. 4J) suggest that following racemic ketamine infusion, the *R*-enantiomer was produced slower with a lower peak concentration than the *S*-variant (Fig. 4K and L). The simulations for the clinical scenario (Fig. 5) show plasma concentrations of norketamine (red line) and HNK (purple line) that eventually exceed ketamine concentrations.

DISCUSSION

In this study the plasma concentrations of ketamine and three of its most important metabolites, norketamine, DHNK and HNK, following escalating doses of racemic ketamine and esketamine, were quantified and analyzed using a population pharmacokinetic model. While often not considered clinically relevant, the importance of the metabolite HNK and to a lesser extent DHNK came to light in recent years, as these metabolites may be responsible for a (large) part of the antidepressant properties of ketamine.[5,11] Additionally, HNK has been shown to produce analgesia in rodent pain models, without the schizotypal side effects that obstruct the use of ketamine in chronic pain treatment.[10] An extensive understanding of the pharmacokinetics of ketamine and its metabolites is therefore of importance and will not only increase our knowledge of the pharmacokinetics of ketamine and its metabolites *per se*, but will also allow the design of precise infusion schemes for specific indications.

Ketamine is extensively metabolized in the liver.[17] The major metabolic pathway is through *N*-demethylation by hepatic enzymes CYP2B6 and CYP3A4 into norketamine.[6,8] Norketamine is subsequently metabolized to HNK by CYP2B6 and CYP2A6 enzymes or to DHNK by CYP2B6 (dehydrogenation). Furthermore, some DHNK may be produced from HNK through dehydration. Minor metabolic pathways that produce low abundance metabolites include hydroxylation of ketamine to hydroxyketamine or hydroxyphenylketamine.[11] Given the relative unimportance of these minor pathways, we modelled the major metabolic ketamine pathway and assumed that DHNK and HNK are both produced from norketamine in a 30:70 ratio. The resultant pharmacokinetic model (Fig. 2) was able to adequately describe the concentration time data of the stereoisomers of ketamine, norketamine and DHNK, and the sum of *R*- and *S*-HNK. Total HNK was modelled as we were unsuccessful in measuring the individual HNK stereoisomers. Still, we were able to predict *S*- and *R*-HNK formation in our simulations (Fig. 4K and L). We did not model DHNK formation from HNK as we assumed that just minute quantities of HNK were transformed into DHNK. Additionally, adding this metabolic pathway would have increased the complexity and therefore decreased stability of the model with consequently less reliable parameter estimates.

Our analysis indicates major differences in *S*- and *R*-enantiomer pharmacokinetics, irrespective of their origin, with significant higher concentrations of *R*-ketamine, *R*-norketamine and *R*-DHNK than the corresponding *S*-enantiomers (Fig. 1). This corresponded with an up to 50% reduced elimination clearance of the *R*- compared to the *S*-enantiomers. It is generally accepted that *S*-enantiomer metabolism is favored over *R*-enantiomer metabolism and is partly explained by the higher affinity of the CYP3A4 enzyme for *S*-ketamine. [5,18-21] Similar *S*- and *R*-enantiomer profiles were reported by Zhao et al.[11] They studied nine patients with treatment-resistant bipolar depression

following daily treatment with 0.5 mg/kg racemic ketamine given over 40 min, on three subsequent days. Zhao et al. analyzed concentration-time data during the initial 230 min following RS-ketamine administration as well as on the subsequent 3 days post infusion (in total 9 samples per subject were obtained) and constructed a population pharmacokinetic model that was made up of three ketamine, two norketamine and single HNK and DHNK compartments (no metabolism compartments were included). Similar to our data they observed an S:R concentration ratio < 1 for ketamine and DHNK, while no enantioselectivity was observed for norketamine. Alike our analysis, only total HNK was measured in the study of Zhao et al.[11] In contrast to our study, they observed that DHNK was the main metabolite in 4 of their subjects, norketamine in 3 and HNK in 2 subjects. In our study, total plasma HNK concentrations were approximately two times higher than the sum of *S*-and *R*-DHNK, which suggests that HNK formation is favored over DHNK formation during the first 5 hours following ketamine administration. Possibly the higher DHNK production observed by Zhao et al. was related to the longer sampling times.

A clinical important observation from the simulation study (Fig. 5) is that following a similar ketamine dose of 0.5 mg/kg given over 40 min (the dose used in the treatment of therapy-resistant depression), racemic ketamine HNK plasma concentrations are higher than following *S*-ketamine administration, *i.e.* the sum of *R*- and *S*-HNK concentrations after racemic ketamine exceeds *S*-HNK concentrations after *S*-ketamine administration. This suggests that when higher HNK concentrations are needed to improve treatment efficacy, the racemic formulation is to be preferred over *S*-ketamine. Additionally, from the simulation we infer lower *R*- than *S*-HNK concentrations, which we attribute to the slower formation of *R*-HNK. In rats, Moaddel et al. show higher (2*S*,6*S*)-HNK concentrations after *S*-ketamine infusion compared to (2*R*,6*R*)-HNK after *R*-ketamine infusion.[22] These data agree with our simulation data. However, a major limitation of our study is the restriction of HNK concentration data to 5 hours following the start of ketamine infusion. As a consequence, we may have missed peak HNK data occurring at later times. Hence, we cannot draw definite conclusions regarding a possible difference in *R*- and *S*-HNK pharmacokinetics in our data set.

Previous studies suggested differences in *S*-ketamine pharmacokinetics after administration *S*-ketamine *vs* racemic ketamine, due to the inhibition of *S*-ketamine metabolism by the *R*-enantiomer.[20] We were unable to detect significant differences in *S*-ketamine pharmacokinetics after either formulation. Hence, the clinical relevance of formulation (*i.e.* a formulation with or without *R*-ketamine) on *S*-ketamine pharmacokinetics therefore remains debatable.

In two arms of the study, we infused SNP. This was done to evaluate a possible modifying effect of SNP on the ketamine-induced schizotypal effects.[13] Additionally, SNP may reduce blood pressure elevations that coincide with ketamine treatment due

to ketamine-induced sympathoexcitation.[13] Importantly, SNP will cause vasodilation that may lead to increased distribution of ketamine. The observed increases in terminal and intercompartmental clearances were moderate (effect on ketamine CL and Q 9% and 22%, respectively) and were restricted to ketamine. Based on the simulations (Fig. 4), the effect of SNP on the complete pharmacokinetic picture seems limited. This further supports our hypothesis that the mitigating effect of SNP on psychotomimetic side effects of racemic ketamine is not pharmacokinetically driven but is related to the restoration of ketamine-induced depletion of intracellular nitric oxide, which restores neuroprotective effects from NMDAR activation.

The study has several limitations that warrant further commenting. First, the central volumes of distribution for all metabolites were set equal to the ketamine central volume of distribution. This was needed due to non-identifiability of these metabolite compartments. This might introduce bias to the estimation of metabolite clearances and peripheral compartment volumes. Administration of the metabolites or measurement of (glucuronide)-metabolites in urine could help solve this problem. However, norketamine, DHNK and HNK are currently not available for human use. Second, we were unable to estimate the parent fraction converted into metabolites. In agreement with other studies, we assumed that ketamine was fully transformed into norketamine.[9,12,14] This assumption may have influenced the parameter estimates of the formation of secondary metabolites from norketamine. The assumption of a 30%:70% ratio (DHNK:HNK) is based on the measured plasma concentrations and was needed to overcome structural parameter un-identifiability. Although modification of the formation ratio resulted in a change in DHNK and HNK clearances and HNK peripheral volume of distribution proportional to the different ratios used for DHNK and HNK formation, no effects on the objective function were observed. Third, the 5-h sampling time may have been sufficient for reliable estimation of ketamine and norketamine model parameters, but as indicated above, this time profile may have been insufficient to properly characterize the pharmacokinetics of the secondary ketamine metabolites. Sampling up to 24-48 hours post-dose would be likely to obtain sufficient data on secondary metabolite kinetics. Possibly, the estimate of the high DHNK elimination clearance estimate was related to this issue. Since no second compartment could be estimated for DHNK, no intercompartmental clearance parameter was estimated. Conceivably, the elimination clearance may be the sum of a (non-identified) intercompartmental clearance and the elimination clearance. Additionally, fixing the DHNK formation rate to 30% of the norketamine elimination rate may have overestimated the DHNK metabolic pathway.

CONCLUSIONS

We performed a population pharmacokinetic modeling study of ketamine and its major metabolites. Differences in pharmacokinetics between formulations and enantiomers were identified. Most importantly, we observed differences between *S*- and *R*-enantiomer elimination clearances. Another relevant observation was the absence of significant clinical effect of SNP on ketamine pharmacokinetics. This indicates that our previous finding of lesser psychotomimetic side effects when racemic ketamine is combined with SNP is not pharmacokinetically driven.[13] Despite some limitations, our model is likely to be of sufficient quality to be used in future pharmacokinetic and pharmacodynamic studies into the efficacy and side effects of ketamine and metabolites.

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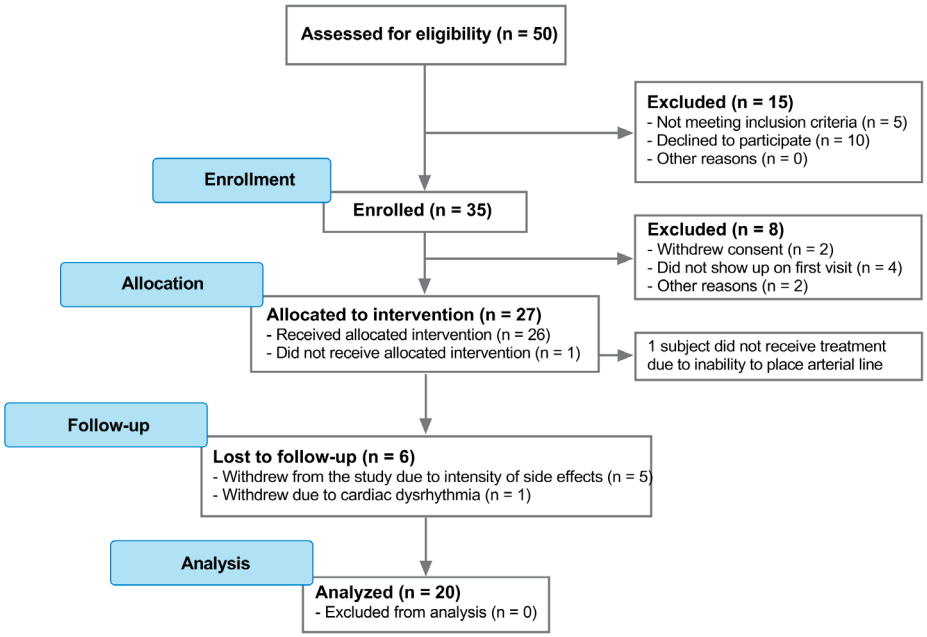
SUPPLEMENTAL DATA

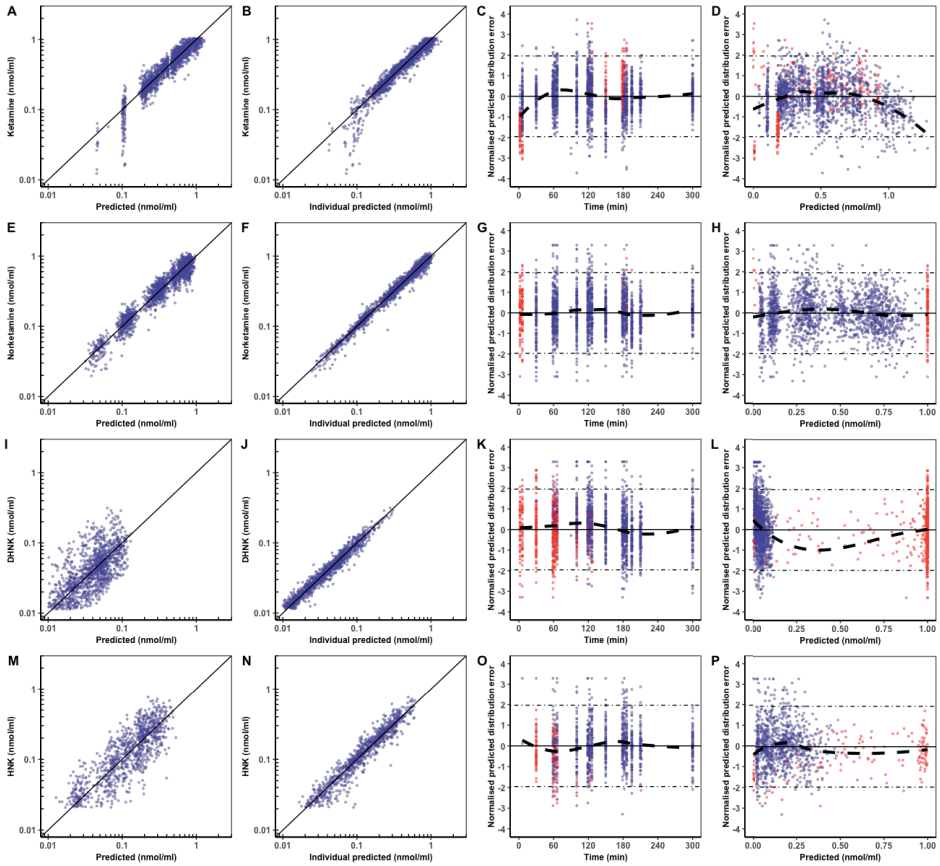
Supplemental Table 1. Mean peak concentrations of individual analytes

Analyte	C_{MAX} ± SD (nmol/mL)	T_{MAX} ± SD (min)
Esketamine		
S-Ketamine	1.111 ± 0.160	170 ± 19
S-Norketamine	0.876 ± 0.130	187 ± 5
S-DHNK	0.050 ± 0.018	270 ± 45
S-HNK	0.221 ± 0.058	251 ± 59
Racemic ketamine		
S-Ketamine	1.115 ± 0.105	173 ± 18
S-Norketamine	0.840 ± 0.107	190 ± 12
S-DHNK	0.054 ± 0.018	253 ± 57
R-Ketamine	1.211 ± 0.117	170 ± 19
R-Norketamine	0.975 ± 0.134	187 ± 9
R-DHNK	0.099 ± 0.032	290 ± 30
RS-HNK*	0.363 ± 0.125	242 ± 56

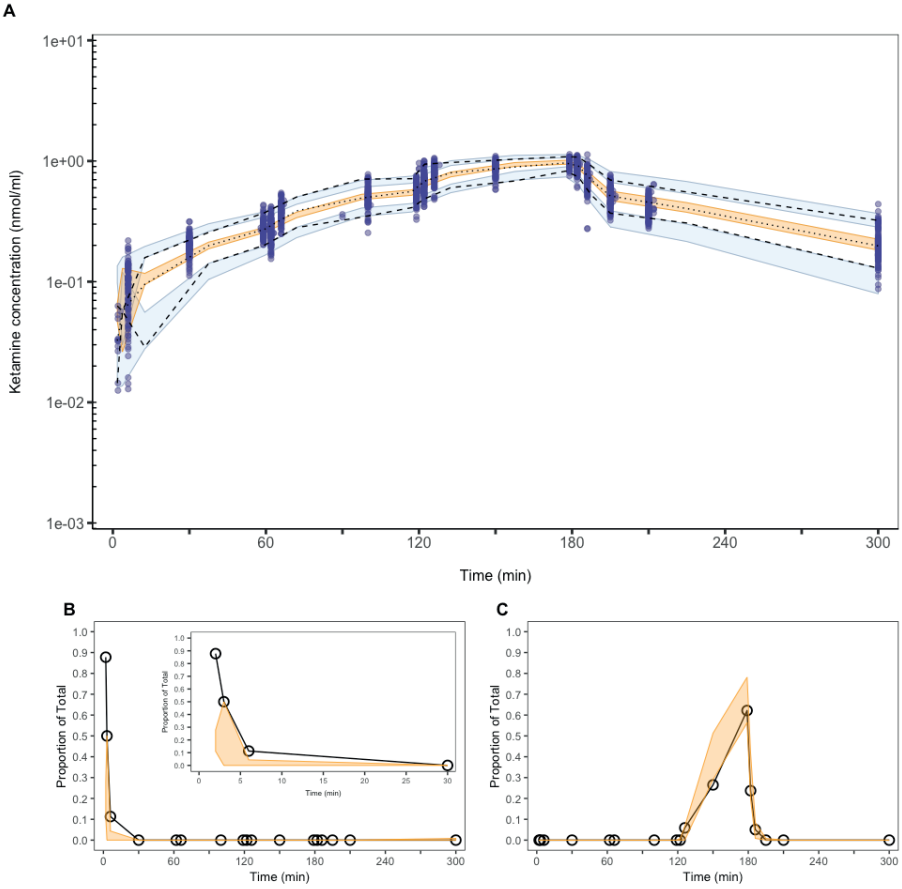
Maximum concentrations of the individual isomers after administration of either esketamine or racemic ketamine. C_{MAX} = mean peak concentration; SD = standard deviation; T_{MAX} = mean time at which concentration is C_{MAX}. *Total HNK concentration.



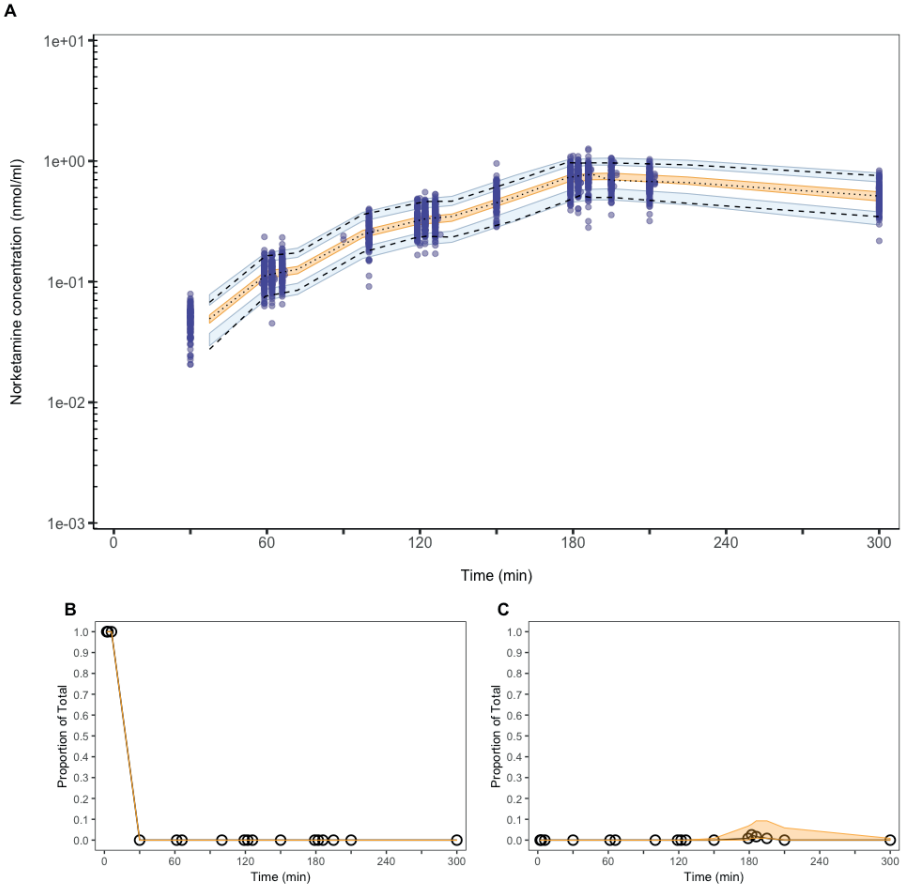
Supplemental Figure 1. Consort flowchart



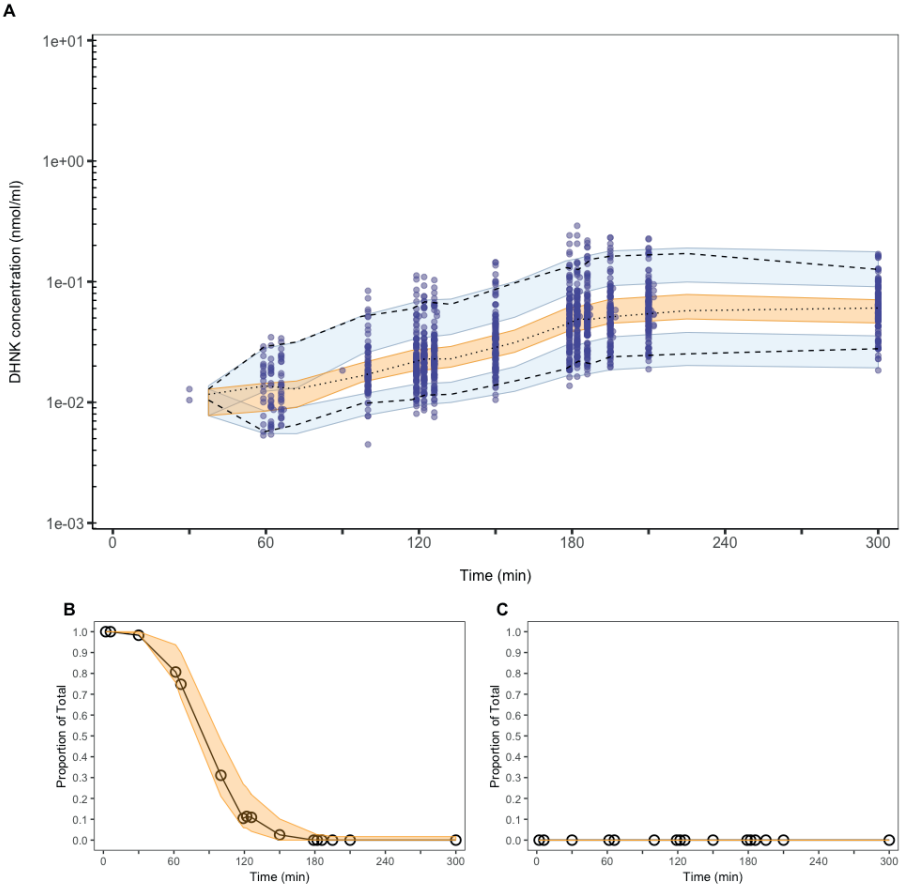
Supplemental Figure 2. Goodness of fit plots. Predicted *versus* measured data, individual predicted *versus* measured data, normalized prediction distribution error *versus* time and normalized prediction distribution error *versus* predicted plots for pooled ketamine (**A-D**), norketamine (**E-H**), DHNK (**I-L**) and HNK (**M-P**) data. Data points below the lower limit of quantitation and above the upper limit of quantitation are shown in red in the normalized prediction distribution error panels.



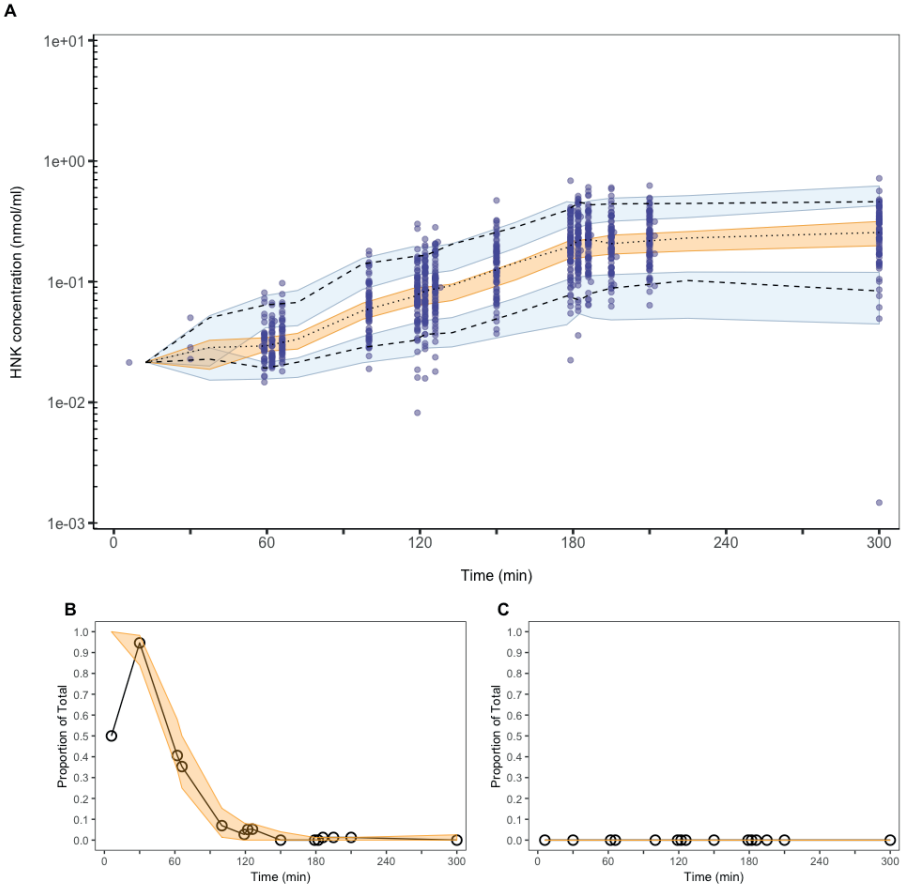
Supplemental Figure 3. Prediction-variance-corrected visual predictive checks for pooled ketamine data (**A**). The dots represent the observed data. The dashed lines represent the 5th and 95th percentiles of the observed data. The median of the observed data is shown by the dotted line. The 95% prediction intervals of the 5th and 95th percentiles and median of the simulated data are shown by the shaded areas. Visual predictive checks for data below the limit of quantitation (**B**) and above the upper limit of quantitation (**C**). The black dots and line represent the proportion BLQ (**B**) or ULOQ (**C**) data points in the observed data. The 95% prediction interval of the proportion in the simulated data is shown by the shaded area.



Supplemental Figure 4. Prediction-variance-corrected visual predictive checks for pooled norketamine data (**A**). The dots represent the observed data. The dashed lines represent the 5th and 95th percentiles of the observed data. The median of the observed data is shown by the dotted line. The 95% prediction intervals of the 5th and 95th percentiles and median of the simulated data are shown by the shaded areas. Visual predictive checks for data below the limit of quantitation (**B**) and above the upper limit of quantitation (**C**). The black dots and line represent the proportion BLQ (**B**) or ULOQ (**C**) data points in the observed data. The 95% prediction interval of the proportion in the simulated data is shown by the shaded area.



Supplemental Figure 5. Prediction-variance-corrected visual predictive checks for pooled dehydronorketamine data (**A**). The dots represent the observed data. The dashed lines represent the 5th and 95th percentiles of the observed data. The median of the observed data is shown by the dotted line. The 95% prediction intervals of the 5th and 95th percentiles and median of the simulated data are shown by the shaded areas. Visual predictive checks for data below the limit of quantitation (**B**) and above the upper limit of quantitation (**C**). The black dots and line represent the proportion BLQ (**B**) or ULOQ (**C**) data points in the observed data. The 95% prediction interval of the proportion in the simulated data is shown by the shaded area.



Supplemental Figure 6. Prediction-variance-corrected visual predictive checks for pooled hydroxynorketamine data (**A**). The dots represent the observed data. The dashed lines represent the 5th and 95th percentiles of the observed data. The median of the observed data is shown by the dotted line. The 95% prediction intervals of the 5th and 95th percentiles and median of the simulated data are shown by the shaded areas. Visual predictive checks for data below the limit of quantitation (**B**) and above the upper limit of quantitation (**C**). The black dots and line represent the proportion BLQ (**B**) or ULOQ (**C**) data points in the observed data. The 95% prediction interval of the proportion in the simulated data is shown by the shaded area.

5

Stereoselective ketamine effect on cardiac output: *A population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers*

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Ketamine exhibits a plethora of significant adverse effects, including those on the cardiovascular system.[1] While ketamine has a direct negative inotropic effect, activation of the sympathetic system causes the release of catecholamines, vagal inhibition, noradrenaline release from sympathetic ganglia and inhibition of noradrenaline reuptake at neuronal and non-neuronal tissue (including the myocardium).[2-4] As a consequence, ketamine will induce cardiodepression when noradrenaline stores are depleted or cardiovascular excitation after administration of anesthetic doses of ketamine (often a short period of cardio-depression precedes excitation) and after low or subanesthetic doses of ketamine, used in the treatment of acute and chronic pain. Cardiovascular excitation is characterized by systemic and pulmonary hypertension, tachycardia and increases in cardiac output, all combined with an increase in myocardial oxygen consumption. Cardiodepression may be partially explained by a decrease in intracellular Ca^{2+} levels, due to the ketamine-induced inhibition of Ca^{2+}-release from intracellular stores and inhibition of the L-type voltage gated Ca^{2+}-channels.[5,6] The exact mechanism of ketamine-induced sympathoexcitation is not known but may be related to sodium channel blockade in parasympathetic centers in the brainstem and in spinal cord neurons.[7] Additionally, the reduction of intracellular nitric oxide concentrations has been proposed as mechanisms of sympathicoexcitation.[8]

In the current study, we examined the effect of racemic- (containing both *R*- and *S*-ketamine) and separately *S*-ketamine and their most relevant metabolites norketamine (NK), dehydronorketamine (DHNK) and hydroxynorketamine (HNK) on cardiac output, in a population of healthy volunteers. We analyzed the data using a population pharmacokinetic/pharmacodynamic modeling approach to separate the effects of *S*- and *R*-ketamine (and metabolites) on cardiac output. This study is part of a larger project in which the effect of nitric oxide donor sodium nitroprusside (SNP) on racemic (*RS*)- and *S*-ketamine-related adverse effects is studied. We previously reported that SNP reduces ketamine-induced schizotypal adverse effects following *RS*-ketamine but not following *S*-ketamine, suggestive of an SNP effect on a pathway activated by the *R*-ketamine isomer.[9] More recently, we published a pharmacokinetic model of ketamine and its metabolites and concluded that the SNP effects were not induced by changes in ketamine pharmacokinetics.[10] Our current analysis is aimed at determining the separate effects of *S*- and *R*-ketamine isomers and related metabolites on cardiac output and determine whether SNP has a mitigating effect of ketamine-induced cardiovascular excitatory effects.

METHODS

Ethics and subjects

This study is part of a large project on the ability of SNP to reduce *RS*- and *S*-ketamine ketamine-induced side effects. Apart from the primary analysis,[9] three separate secondary analyses were pre-planned: (1) development of a population pharmacokinetic model of *RS*- and *S*-ketamine and metabolites;[10] (2) development of a pharmacodynamic model of the analgesic and schizotypal side effects of *RS*- and *S*-ketamine; and finally, (3) development of a population pharmacodynamic model that describes the changes induced by *RS*- and *S*-ketamine on cardiac output and effect of SNP. Here, we report the results of the last analysis. The medical ethic committees of the Leiden University Medical Center (Medisch Ethische Toetsingscommissie Leiden, Den Haag, Delft) approved the study protocol, that was registered at the trial registry of the Dutch Cochrane Center (www.trialregister.nl) under registration number 5359. All study procedures followed the latest version of the Good Clinical Practice guidelines and the Declaration of Helsinki. The subject selection process can be found in Ref. 9. In brief, inclusion criteria were healthy male subjects, aged 18-35 years and body mass index of 19-30 kg/m^2. They were all screened and only after their history and physical examination (incl. negative drug tests) did not yield any abnormalities, the subjects were enrolled in the study. Subjects were not allowed to consume caffeinated food or drinks or consume any grapefruit containing products in the day and week, respectively, before dosing.

Study design

The study had a double-blind, randomized, 4-way crossover design. All subjects received escalating intravenous doses of intravenous *RS*-ketamine (Ketalar, Pfizer Pharma, Berlin, Germany) on visits A and B and escalating doses of *S*-ketamine (Ketanest, Eurocept BV, Ankeveen, the Netherlands) on visits C and D. On visits A and C, SNP was infused at a dose of 0.5 mg/kg per min, while placebo (NaCl 0.9%) was infused on visits B and D. *RS*-/*S*-ketamine and SNP/placebo were administered *via* two sperate infusion lines placed on opposing arms. The order of visits was randomized using a computer-generated, randomization list based on a four-block design (www.randomization.com). Blinding procedures, allocation and dispensing are described elsewhere. The researchers were unblinded after all experiments were concluded (August 24, 2017).

RS-ketamine and S-ketamine were dosed as follows: *RS*-ketamine 60 min 0.28 mg.kg^{-1}.h^{-1}; 60-120 min 0.57 mg.kg^{-1}.h^{-1} and 120-180 min: 1.14 mg.kg^{-1}.h^{-1}; *S*-ketamine was 0-60 min: 0.14 mg.kg^{-1}.h^{-1}, 60-120 min: 0.28 mg.kg^{-1}.h^{-1} and 120-180 min: 0.57 mg.kg^{-1}.h^{-1}. These doses were considered equipotent in terms of analgesic effect.[9] Arterial blood samples were obtained from an arterial line at the following times relative to the start of drug infusion (t = 0): t = 2, 6, 30, 59, 62, 66, 100, 119, 122, 126, 150, 179,

182, 186, 195 , 210 and 300 min. Plasma samples were analyzed in the laboratory of dr. Evan Kharasch as described by Rao et al.[11] Following *RS*-ketamine administration, the plasma concentration of *S*- *and R*-ketamine , *S*- *and R*-norketamine and *S*- *and R*-dehydronorketamine (DHNK), and total (*S* + *R*) hydroxynorketamine (HNK) were measured. Cardiac output was measured from the arterial pressure wave (obtained from the arterial cannula) using the FloTrac sensor and Vogileo. Cardiac output values were averaged over 1-minute intervals for further analysis.

Population pharmacokinetic-pharmacodynamic analysis

NONMEM version 7.4.4 (ICON Development Solution, Hanover, Maryland) was used for the data analyses. The plasma concentration – cardiac output data were analyzed by a two-step pharmacokinetic-pharmacodynamic approach. First a pharmacokinetic model was developed as described previously.[10] In brief, a seven-compartment PK model was constructed to describe the pharmacokinetics of ketamine, norketamine, DHNK enantiomers and total HNK. The central compartment of a two-compartmental ketamine model was linked *via* 2 metabolic (or delay) compartments to the central compartment of a two compartmental norketamine model. Since norketamine is further metabolized to either DHNK and HNK, the central norketamine compartment was linked to the DHNK disposition compartment *via* one metabolic (or delay) compartment; HNK was modeled with a two compartmental model, of which the central compartment was linked to the central norketamine compartment without a delay compartment. See also Figure 2 of Ref. 10.

In the second step, the empirical Bayesian estimates obtained from the pharmacokinetic analysis were used as input for the (cardiac output) pharmacodynamic model. Random effects were included in the model to account for interindividual variability and inter-occasions variability (IOV), as follows: $\theta_i = \theta \times \exp(\eta_i + \eta_{iov})$, where θ_i is the parameter for individual i, θ the population parameter, η_i is the random difference between the population and individual parameter and η_{iov} the difference between θ_i and θ due to inter-occasion variability.

To test the potential effect of each compound, we started with a base pharmacodynamic model that just included *S*-ketamine, which was sequentially expanded by adding its metabolites, and next *R*-ketamine and its metabolites. The total effect on cardiac output was defined as the sum of effects calculated for each compound. Compounds were only included in the pharmacodynamic model, when addition gave a significant ($p < 0.01$) improvement of the objective function value as calculated by NONMEM. To evaluate a potential hysteresis between ketamine and metabolite plasma concentrations and observed effects, postulated effect compartments were tested for each individual included compound (*i.e.* we tested whether effect equilibration compartments improved the objective function value). It was assumed that the effect compartment

equilibrates with the central plasma compartment with rate constant ke0 with effect half-time $t_{1/2} = \ln(2)/k_{e0}$.

A linear pharmacodynamic model was initially developed to describe the plasma concentration-cardiac output data (*i.e.* the base model): YF = BLN * (1 + YE_{SUM}) + ε, where YF is the cardiac output value predicted by the model, BLN is the baseline cardiac output, YE_{SUM} the sum of the effects on the cardiac output caused by ketamine and its metabolites (*i.e.* $YE_{SUM} = YE_{X1} + \ldots\ldots + YE_{X7}$) and ε the residual error. The individual effect of each compound on cardiac output was defined by $YE_{Xn} = 0.25 \cdot (C_{Xn} / C_{25Xn})^{\gamma}$, where YE_{Xn} is the effect of compound Xn on cardiac output, γ the Hill coefficient, C_{Xn} the drug concentration, C_{25Xn} is the effect-site concentration of compound Xn that leads to a 25% change of cardiac output relative to baseline (25% is in the midst of the observed changes) of compound Xn contributing to changes in total cardiac output, where Xn ranges from X1 to X7 with X1 *S*-ketamine, X2 *R*-ketamine, X3 *S*-NK, X4 *R*-NK, X5 *S*-DHNK, X6 *R*-DHNK and X7 total HNK. Note that C_{Xn} could be either the drug concentration in the central volume of distribution, or in the effect compartment, depending on the compound.

Since an undershoot was observed in the cardiac output data following termination of ketamine infusion, a control mechanism was added to the model: YF = BLN * (1 + YE_{SUM} – YC) and τ dYC/dt = (YE_{SUM} – YC), where YC is the output of the controller that counteracts YE_{SUM} with time constant τ. In addition, since in some subjects the residuals of the data fits were correlated, a parallel process noise component (*i.e.* Kalman filter) was added to the model: $dYC = (YE_{SUM} - YC)/\tau \cdot dt + \sigma\nu \cdot dw$, where $\sigma\nu$ is the standard deviation of the noise component (with units $L \cdot min^{-1} \cdot min^{-0.5}$) and dw a stochastic (Wiener process), with units for w $min^{0.5}$. Finally, a trend parameter (TRD) was added to the model, because a clear increasing trend, irrespective of ketamine or metabolite concentrations, was observed: YF = BLN * (1 + YE_{SUM} – YC + TRD * t/300), where t is the time from the start of the experiment in minutes.

Model selection was based on significant improvements in the objective function value (-2LogLikelihood with $p < 0.01$ following a χ^2-distribution) and by assessment of individual model fits and goodness of fit plots (population predicted *versus* observed, individual predicted *versus* observed, conditional weighted residuals *versus* time and conditional weighted residuals *versus* population predicted plots) and the visual predictive checks. Additionally, auto- and cross-correlation plots were assessed to evaluate model goodness of fit. The correlation between two residuals shifted in time can be described by an auto-correlation function, in which residuals are uncorrelated (so called *white* residuals) when the auto-correlation function is equal to zero, with the exception when t = 0. In addition, the correlation between the residuals and input (*i.e.* the model output, before being inputted in the Kalman filter) shifted in time, can be described by the cross-correlation function. Similar to the auto-correlation function, if the

cross-correlation function equals zero, this indicates that the residuals are completely random, and the model therefore explains the data completely.[12]

Since a large number of combinations could be tested due to the potential effects of seven different compounds and the incorporation of the TRD parameter, Controller and Kalman filter in the model, we here only describe the most important model combinations. Sequential testing with ketamine and metabolites was performed for five models:

Model 1: base model with just the Kalman filter (no trend parameter or controller); note that when $YE_{SUM} = 0$ the controller is deactivated;
Model 2: model 1 + trend parameter;
Model 3: model 1 + controller;
Model 4: model 1 + trend parameter + controller; and
Model 5: model 2 without the Kalman filter.

The controller relates the undershoot in cardiac output after ketamine infusion ended, the trend term relates to a slow increase in cardiac output over time, and the Kalman filter to the noise in the data.

Finally, potential covariates were tested on the best model, by an automated stepwise covariate screening algorithm (Stepwise Covariate Model building module from Pearl speaks NONMEM).[13] Tested covariates were: (i) *S*- or *RS*-ketamine administration and (ii) placebo or SNP administration. First a forward search was performed, adding covariates to the model that caused a significant drop ($p < 0.01$) of the objective function value. Potential covariates were added to the model parameters in a linear relation, described as: $\theta_i = \theta_{ref} \times (1 + \theta_{COV})$, where θ_{ref} is the typical parameter value for a subject belonging to the reference category of the covariate and θ_{COV} the effect of belonging to the non-reference category. Once covariates caused no further drop in objective function value, the backward search was started. In this step, covariates were sequentially removed from the model. When removal caused a significant reduction of the objective function value ($p < 0.001$), the covariate was retained in the model. This process was continued until all covariates were excluded or until no more covariates were left to exclude. To limit the risk of including irrelevant covariates, the backward search was performed with a more stringent selection criterion.

RESULTS

All twenty subjects successfully completed the study without serious adverse effects. Mean ± SD (range) subject age was 23 ± 2(19-28) years, height 186 ± 6 (175-193) cm, body weight 83 ± 9 (60-98) kg and body mass index 24 ± 2.1 (19.5-28.4) kg/m^2. Cardiac

output data were obtained from all subjects, except from subject 19. We did not collect cardiac output data on one occasion due to failure of insertion of the arterial line. Mean cardiac output *versus* time curves are shown in Figure 1.

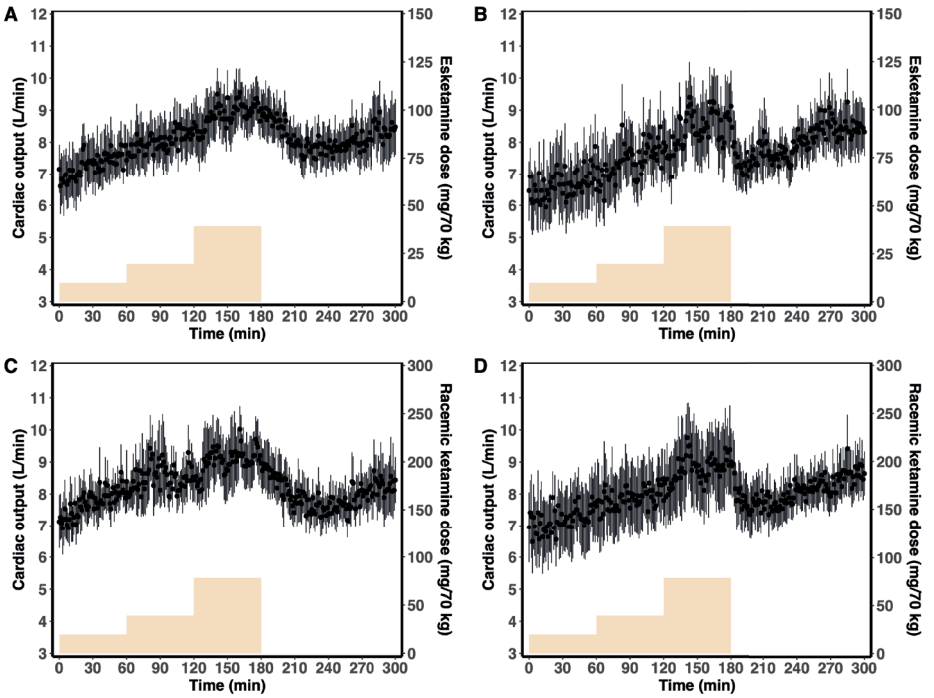

Figure 1. Mean time-cardiac output curves after *S*-ketamine with either placebo or sodium nitroprusside (SNP) co-administration (**A, B**) and after *RS*-ketamine with either placebo or SNP co-administration (**C, D**). Data are mean ± SD. Ketamine doses are given in yellow (right y-axis).

Pharmacodynamic models

Starting with model 1 (base model with Kalman filter, absolute objective function value 24,517), adding the trend term resulted in a ΔOFV of -74 points (model 2). No significant improvement was observed when the controller was added to model 1 (model 3). Since the structure of model 2 best described the data, we limit the description of the sequential compound testing to model 2. The effect of *S*-ketamine on cardiac output was best modeled by adding an effect compartment (ΔOFV of -9.41 points). Sequential expansion of the model with metabolites only showed a significant effect of *S*-norketamine (ΔOFV of -18 points), but, in contrast to *S*-ketamine, reducing cardiac output. Adding *R*-ketamine or its metabolites did not cause a significant improvement of the model and these were therefore not incorporated. Finally, adding an S-norketamine effect compartment improved the model (ΔOFV of -11 points). In agreement with these findings,

sequential compound testing of models 1, 3-5 failed to show significant metabolite effects, indicating that the trend term and controller did not obfuscate potential metabolite effects on cardiac output. Removal of the Kalman filter from the final model 2 resulted in an increase in objective function value by 5986 points and rather large ω^2 values, indicating that the Kalman filter significantly improved the model.

Pharmacodynamic parameters of the final model (model 2) are given in Table 1 with best, median and worst data fits in Figure 2. The *S*-ketamine concentration causing an increase in cardiac output by 25% was 1.68 ± 0.45 nmol/mL. The *S*-ketamine blood-effect-site equilibration half-life ($t½k_{e0}$) was 2.28 ± 0.64 min, the time constant of the noise component was 31.4 ± 7.9 min and the value of the trend term 0.38 ± 0.08 L/300 min (*i.e.* a 380 ml/min increase in ventilation over the course of the study). In addition, the *S*-norketamine concentration causing a 25% reduction of cardiac output, was 0.67 ± 0.22 nmol/mL, with an equilibration half-life of 29.3 ± 16.4 min.

Table 1. Pharmacodynamic parameters estimates of model 2

	Typical parameter value (SEE) [%CV]	**Inter-individual variability % (SEE) [%CV]**	**Inter-occasion variability % (SEE) [%CV]**
Baseline cardiac output (L/min)	6.8 (0.2) [3]	11.3 (3.4) [29]	9.7 (1.5) [15]
γ	1 FIX	-	26.4 (8.7) [33]
Trend term (L/min^2)	0.384 (0.081) [21]	17.1 (3.4) [20]	-
C_{25} *S*-ketamine (nmol/ml)	1.68 (0.45) [27]	93.8 (20.6) [22]	-
C_{25} *S*-norketamine (nmol/ml)	0.673 (0.215) [32]	-	
S-ketamine $t_{1/2}k_{e0}$ (min)	2.28 (0.64) [28]	-	-
S-norketamine $t_{1/2}k_{e0}$ (min)	29.3 (16.4) [56]		
τ of the noise component (min)	31.4 (7.9) [25]	-	-
$\sigma\nu$ (L · min^{-1} · min $^{-0.5}$)	0.89 (0.05) [6]	22.9 (2.7) [12]	25.4 (3.6) [14]
$\sigma\in$ (L/min)	0.037 (0.004) [10]	-	35.9 (4.3) [12]

γ is a shape parameter, TRD is a trend term; C_{25} *S*-ketamine is the *S*-ketamine plasma concentration that causes an 25% increase in cardiac output; C_{25} S-norketamine is the *S*-norketamine plasma concentration that causes 25% of the maximum (100%) counteracting effect on the S-ketamine effect; $t_{1/2}k_{e0}$ is the plasma effect compartment equilibrium half-life; τ is the time constant of the noise compartment; $\sigma\nu$ and $\sigma\in$ are the standard deviations of the process and measurement noise components respectively. SEE is the standard error of the estimate and CV the coefficient of variation.

Goodness of fit plots and the visual predictive check for model 2 are given in Figures 3 and 4. Auto-correlation function plots for models 2 and 5 are shown in Fig. 5. The visual predictive check revealed a slight undershoot of the simulated 5th percentile data

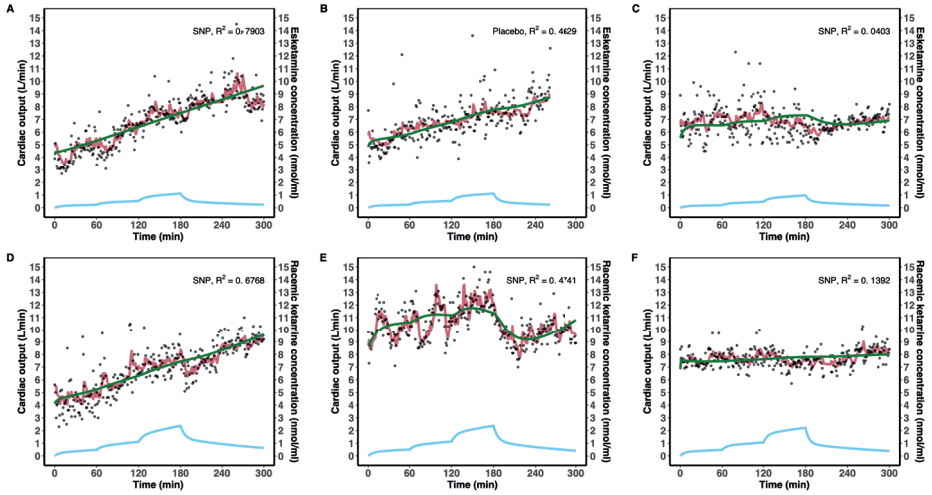

Figure 2. Pharmacodynamic model fits. Best (**A**), median (**B**) and worst (**C**) cardiac output model fits after esketamine administration and best (**D**), median (**E**) and worst (**F**) cardiac output model fits after racemic ketamine administration. The dots are the measured data, the red and green lines the output of models 2 (with Kalman filter) and 5 (without Kalman filter), respectively. The blue lines are the simulated *S*-ketamine concentrations (right y-axis), based on the empirical Bayesian estimates obtained from Kamp et al.[10]

compared to that of the 5th percentile of the true data (lower black line and shaded area). Adding the Kalman filter improved the model fits and resulted in substantially improved goodness-of-fit plots, visual predictive checks (data not shown) and auto- and cross-validation values. This indicates that model 2 has uncorrelated residuals and is to be preferred over model 5. Finally, screening model 2 for covariates failed to show significant effects of either ketamine administration form (*e.g. S*-ketamine *versus RS*-ketamine administration) or placebo *versus* SNP administration.

DISCUSSION

We observed a stereoselective effect of ketamine on cardiac output. While *S*-ketamine increased cardiac output in a concentration-dependent manner, no effect of *R*-ketamine on cardiac output was detected in our data set. Additionally, we observed that, in contrast to *S*-ketamine, its active metabolite *S*-norketamine reduced cardiac output. There was no effect of the nitric oxide donor sodium nitroprusside on the effect of either *S*- or *RS*-ketamine.

Two earlier pharmacokinetic-pharmacodynamic studies on the effect of ketamine on cardiac output were published. Sigtermans et al. administered increasing doses of *S*-ketamine to healthy volunteers and modelled the effect of *S*-ketamine and *S*-norket-

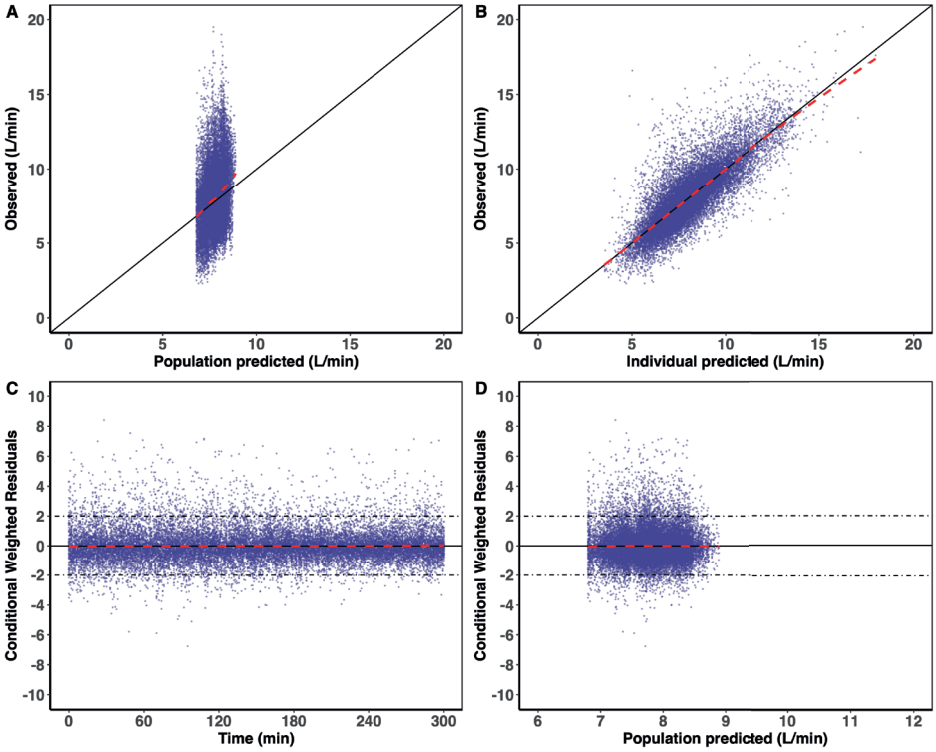

Figure 3. Goodness of fit plots. Observed *versus* population predicted cardiac output (**A**), observed *versus* individual predicted cardiac output (**B**), conditional weighted residuals *versus* time (**C**) and conditional weighted residuals *versus* population predicted cardiac output (**D**) for Model 2. Red lines show LOESS smoothers to identify potential trends.

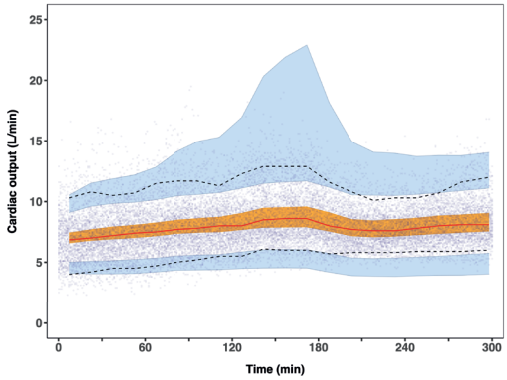

Figure 4. Visual predictive check based on the simulation of 1,000 datasets from model 2. The 50th, 5th and 95th percentiles of the true data are shown by the red and lower and upper black lines respectively. The orange and upper and lower blue shaded areas show the 95% confidence intervals of the simulated 50th (orange) 5th and 95th (blue) percentile data. The dots are the measured cardiac output data.

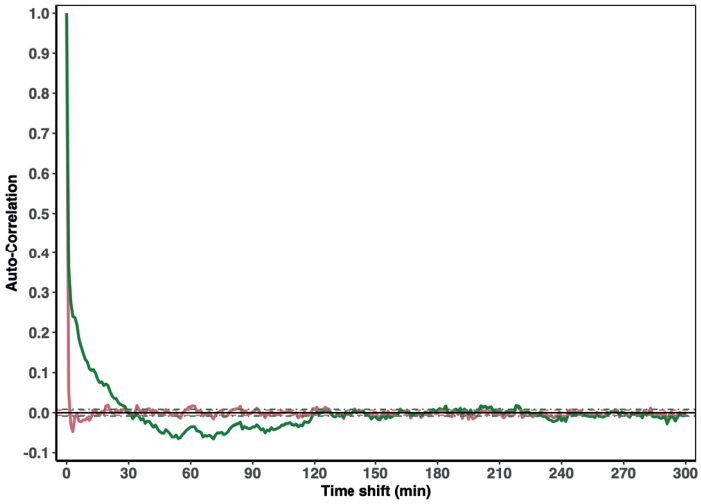

Figure 5. Auto-correlation function of the residuals of Model 2 (red line) and Model 5 (green line) for the total dataset.

amine on cardiac output using a base model with trend term but without controller or noise component.[14] In that study, the increase in cardiac output following infusion of *S*-ketamine was well described by the *S*-ketamine concentration in plasma without any effect from *S*-norketamine. Olofsen et al. administered increasing *S*-ketamine pulsatile doses to healthy volunteers and patients diagnosed with chronic regional pain syndrome type 1.[12] They modelled the effect of just *S*-ketamine on cardiac output using a pharmacodynamic model with controller and noise component. In the current pharmacodynamic analyses incorporation of a trend term and noise component (Kalman filter) contributed to the significant improvement of the description of the data (model 2), while adding a controller did not; the negative contribution of norketamine allowed for the characterization of the undershoot in the data.

The trend term described a slow change in effect over time, independent of the plasma ketamine concentration. Sigtermans et al. observed a positive trend term in their study on the effect of ketamine on antinociception.[14] Possibly, the change in cardiac output of +0.38 L/min in 300 min in the current study may be related to the slow increase in concentration of DHNK and HNK. In order to confirm this hypothesis, we performed sequential metabolite effect testing of the base model without and with a trend term but could not detect a significant contribution of either metabolite to the trend term. Other causes for the positive trend may be a slow increase in arterial carbon dioxide concentration due to the respiratory effects of ketamine, or anxiety-related due to the psychedelic effects of ketamine.

In agreement with Olofsen et al. we added a Kalman filter to the base model. The Kalman filter is a method to track the state of a system in the presence of random disturbances. These disturbances are to be distinguished from residual or measurement noise; here they might affect physiological processes related to homeostasis, and because of the inertia of such processes, the disturbances lead to correlated residual noise in addition to the measurement noise. In the current study, auto-correlation (correlation between residuals) and cross-correlation (correlation between residuals and pharmacodynamic input indicate absence of significant correlations in the model with Kalman filter (model 2), while the noise was correlated in the model without Kalman filter (model 5). This indicates a significant improvement in model performance with more reliable estimates of variability and deterministic model parameters. Additionally, data analyses without Kalman filter yielded much larger ω^2 values (data not shown). These findings agree with earlier studies exploring noisy respiratory data and transdermal opioid absorption.[15,16]

The absence of effect of *R*-ketamine on cardiac output agrees with earlier findings of a lesser potency of *R*-ketamine compared to *S*-ketamine on various endpoints. For example, Geisslinger et al. reported significant higher systolic and diastolic blood pressures following *S*-ketamine compared to *RS*-ketamine.[17] Their results suggest that *S*-ketamine is mostly responsible for the observed cardiovascular effects associated with ketamine administration. Hence, *R*- and *S*-enantiomers differentially engage sympathoexcitation, possibly related to differences in receptor activation. For example, *S*-ketamine is about twice as potent as *R*-ketamine in producing voltage and use dependent blockade of the *N*-methyl-D-aspartate receptor.[18] These data agree with observations that *S*-ketamine, at anesthetic doses, is more potent in reducing the electroencephalogram power spectrum compared to anesthetic doses of *R*-and *RS*-ketamine and the difference in analgesic potency between *S*- and *RS*-ketamine at subanesthetic doses.[9,19]

Covariate analysis revealed absence of effects from the administration form (racemic ketamine or the *S*-isomer) or from absence or presence of the nitric oxide donor SNP. This later observation contrasts a study in rabbits that shows that L-arginine, a substrate of nitric oxide formation, attenuated ketamine-induced increased in renal sympathetic nerve activity.[8] Possibly the SNP dose in our study was too low to reduce cardiac output (in contrast to the effect of SNP on psychedelic symptoms). Additionally, compensatory mechanisms may have prevented any effect of low-dose SNP in our healthy and young population of volunteers.

Finally, we observed a negative contribution of *S*-norketamine on cardiac output, an effect that could explain the undershoot following ketamine infusion. In fact, *S*-norketamine counteracted the effect of *S*-ketamine on cardio-excitation. This finding agrees with an earlier modeling study in which norketamine was anti-analgesic and counteracted the analgesic effects of ketamine.[20] The mechanism of this antagonist effect remains unknown, and may be related to a differential receptor activation profile of

norketamine *versus* ketamine.[20] However, as stated earlier, one needs to be rather careful in the interpretation of these finding from our complex modeling study.[20] Additional proof from either animal or human studies is needed before any defensive conclusions regarding the behavior of *S*-norketamine on cardiac output may be drawn.

CONCLUSIONS

In this chapter, we performed a pharmacodynamic modeling study that evaluated the effects of *R*- and *S*-ketamine and its most important metabolites on cardiac output in healthy male volunteers. Important findings were that, in contrast to *S*-ketamine, *R*-ketamine was devoid of effect on cardiac output, while *S*-norketamine counteracted the effect of *S*-ketamine by having a negative effect on cardiac output.

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6

Are the psychedelic and analgesic effects of ketamine independent?

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Submitted

Ketamine is a versatile drug that is used by anesthesiologists, pain physicians and more recently also by psychiatrists.[1] At high dose, ketamine produces a dissociative anesthetic state, while at low (subanesthetic) doses it produces potent analgesia. Additionally, ketamine produces psychedelic effects related to its dissociative properties. At low doses these dissociative effects cause inner feelings and thoughts that do not agree with reality, and misperception of external stimuli such as abnormal alterations of the extremities or aberrant experience of time and surroundings.[2] At increasing doses overt paranoia, hallucinations, severe derealization and depersonalization, and anxiety attacks may occur.[2] Due to these serious adverse effects, pain physicians are often hesitant to consider ketamine for treatment of chronic pain and patient compliance can be low due to fear of dissociation. It has been suggested that ketamine analgesia (and antidepressant properties) is highly associated and possibly even generated by its dissociative effects.[3-5] This would suggest that ketamine (and its metabolites) dissociative and analgesic effects have common pharmacodynamic properties with a similar potency and onset/offset time. However, there is evidence that suggests that the two endpoints are independent. For example, in healthy volunteers, Gitlin et al.[6] recently studied the effect of ketamine on cuff pain intensity and psychedelic symptoms without and with co-administration of midazolam. Their statistical analysis revealed that analgesia was not associated with the dissociative effects of ketamine. This indirect evidence agrees with earlier findings from our laboratory that showed that the nitric oxide donor sodium nitroprusside modestly reduced psychedelic symptoms in volunteers receiving racemic ketamine but not esketamine.[7] Such an effect was not observed for ketamine analgesia (unpublished observation). To determine whether ketamine-induced dissociation and analgesic behavior are independent, we performed a population pharmacokinetic-pharmacodynamic analysis in healthy volunteers.[8] All subjects received increasing doses of racemic ketamine and pain relief to a pressure pain stimulus was measured concomitantly with signs of alterations in perception of external stimuli. Our Null hypothesis is that ketamine pharmacodynamics (potency and onset/offset times) are equal for these two endpoints, an indication that dissociation and analgesia from ketamine are interdependently generated in the brain.

METHODS

Ethics and subjects

The data used in this analysis is part of a larger data set that was used previously to study the effects of sodium nitroprusside (SNP) on ketamine-induced adverse effects,[7] to construct a population pharmacokinetic model of ketamine and its metabolites,[8] and a pharmacodynamic model of ketamine-induced changes in cardiac output.[9] In the

current analysis, we developed a population pharmacodynamic model of ketamine and its metabolite norketamine to describe the relation between racemic (*RS*) ketamine and norketamine plasma concentrations and pressure pain threshold and the change in external perception as measure of ketamine psychedelic effect. The study protocol was approved by the institutional review board (METC LDD, Leiden University Medical Center, Leiden, The Netherlands) and registered at the trial register of the Dutch Cochrane Center (www.trialregister.nl) under registration number 5359. The study was performed in healthy male volunteers aged 18-34 years and a body mass index in between 20 and 30 kg/m^2. Specific inclusion and exclusion criteria are found in Ref. 7.

Study design

The original study was a 4-arm randomized double-blind study during which esketamine or *RS*-ketamine were infused against a background of either SNP or normal saline (placebo).

For the current analysis we used data obtained on a single occasion on which subjects received escalating intravenous doses of *RS*-ketamine (Ketalar, Pfizer, Germany) over 3 hours (first hour 0.28 mg/kg, second hour 0.57 mg/kg and third hour 1.14 mg/kg) against a background of normal saline infusion.

The following data were collected prior and during *RS*-ketamine infusion:

(1) The pain pressure threshold was measured was by applying an increasing pressure to a 1 cm^2 skin area between thumb and index finger, using the FP 100 N Algometer (FDN 100, Wagner Instruments Inc, CT, USA). The applied pressure was gradually increased until the subject indicated when the pressure became painful, after which the pressure was released. The FDN 100 has a force capacity (± accuracy) of 100 ± 2 N and graduation of 1 N. Pressure pain thresholds were obtained before start of the *RS*-ketamine infusion (baseline), followed by measurements at 15 min intervals during and after *RS*-ketamine infusion. Measurements continued until 2 h after termination of the *RS*-ketamine infusion.

(2) External perception was obtained from the Bowdle questionnaire.[10] The Bowdle questionnaire is a validated list of 13 items developed to quantify the psychedelic effects of ketamine in healthy volunteers. The subject is asked to rate each item on a 100 mm visual analogue score that range from "not at all" to "extremely". External perception relates to the misapprehension of external stimuli or the surroundings including body parts and is derived from the following items: my body or body parts seemed to change their shape or position; my surroundings seemed to change in size, depth, or shape; the passing of time was altered; the intensity of colours changed; and the intensity of sound changed. External perception was measured at t = 0 (baseline) and 20, 40, 55, 80, 100, 115, 140, 160, 175, 200, 220, 240, 260 and 280 after the start of ketamine infusion.

(3) Plasma concentrations of *R*- and *S*-ketamine and *R*- and *S*-norketamine. At regular time points (t = 0, baseline) and 2, 6, 30, 59, 62, 66, 100, 119, 122, 126, 150, 179, 182, 186, 195, 210 and 300 min after the start of ketamine infusion) 8 mL blood was drawn from an arterial line placed in the radial artery (opposite to the infusion arm). Plasma samples were measured in the laboratory of dr. Evan Kharasch (Washington University School of Medicine, St. Louis, MO, USA) as described by Rao et al.[11]

Data analysis

Model development

The pharmacokinetic data were analyzed separately and previously reported.[8] From that model, Empirical Bayesian Estimates (EBE's) of the PK parameters were obtained and their fixed values were used as input to the pharmacodynamic model.

Pressure pain threshold (PPT) and external perception (ExP) were simultaneously analyzed in a single model. Pressure pain was modelled as:

$$PPT(t) = BLN * [1 + (C\mathit{RS}\text{-}K(t)/C50\text{-}K)^{\gamma}] \quad \text{Eqn(1)}$$

where PPT(t) is the amount of pressure in Newton applied at which the subjects first reported pain, BLN is the estimated pressure pain threshold at baseline, C*RS*-K the plasma concentration of *RS*-ketamine in nmol/mL (*i.e.* the sum of the *R*- and *S*-isomers), C50-K is the estimated *RS*-ketamine concentration needed to increase the PPT by 50% but analgesia by 100% (in nmol/mL),[12] and γ the Hill coefficient. External perception was described by a sigmoid Emax model:

$$ExP(t) = [Emax * C\mathit{RS}\text{-}K(t)^{\gamma}] / [C50K^{\gamma} + C\mathit{RS}\text{-}K(t)^{\gamma}] \quad \text{Eqn(2)}$$

where ExP is the experienced level of external perception as rated on a 100 mm visual analogue scale, Emax the maximum effect on external perception (100), C50K the *RS*-ketamine concentration in nmol/mL needed to reach 50% of Emax and γ the Hill coefficient. Since external perception was measured on a 100 mm VAS scale, ratings could not be higher than 100 points. We therefore incorporated the M3 data censoring method as published by Beal et al.[13] for the external perception data.

Since we observed a small discrepancy in the individual model fits for ExP and to a lesser extent for PPT during the infusion phase, we postulated that an *RS*-norketamine effect might be present. We therefore added *RS*-norketamine as input to the model, based on a receptor kinetics approach, in which *RS*-norketamine could displace *RS*-ketamine from the receptor. The consequence of this would be a counteracting effect of *RS*-norketamine on the effects of *RS*-ketamine.[14] The effect of *RS*-norketamine was defined as:

EFF*RS*-NK = C*RS*-NK/C100NK Eqn(3)

where C*RS*-NK is the *RS*-norketamine plasma concentration in nmol/mL and C100NK the *RS*-norketamine plasma concentration causing a 100% increase in C50K. So in equations (1) and (2) above, C50K was substituted by

C50KN = C50K * (1 + EFF*RS*-NK) Eqn(4)

To account for a possible delay between plasma concentrations and effect, effect compartments for *RS*-ketamine and *RS*-norketamine were postulated that were assumed to equilibrate with the central compartment with an effect half-time of $t_{1/2} = \ln(2)/k_{e0}$, where k_{e0} is the rate constant.

Covariates

Since pressure pain and external perception were simultaneously analyzed, potential differences in estimated C50 and k_{e0} parameter estimates between PPT and ExP were tested, by using an automated covariate search algorithm (Stepwise Covariate Model building module from PsN), with the measured outcome (*i.e.* pressure pain *vs* external perception) as potential covariate.

The first selection step incorporated a forward selection approach, in which covariates were first one by one added to the model parameters. The parameter – covariate combinations that caused the largest significant ($p < 0.01$) drop in the objective function value (OFV) was added first, followed by other parameter-covariate combinations that caused the next largest significant drop in OFV. This process continued until all parameter-covariate combinations were included in the model or until no more parameter-covariate combinations causing a significant drop in OFV were left.

The final forward model was then used for the backward search. In this step, covariates were removed one by one from the model. Covariates were only retained in the model when removal caused a significant ($p < 0.001$) increase in the OFV. This process continued until no covariates that caused a significant worsening in the OFV were left or until all covariates were removed from the model. For the backward search, a more stringent selection criterium ($p < 0.001$) was used in order to prevent irrelevant parameter-covariate combinations to be included in the model. A linear relation was used to add covariate effects to the model parameters: $\theta_i = \theta_{ref} \times (1 + \theta_{COV})$, with the typical parameter value for a subject with the reference outcome θ_{ref} (pressure pain) and the effect of belonging to the non-reference category θ_{COV} (external perception).

Statistical analysis

Data analysis was performed with NONMEM version 7.4.4 (ICON Development Solution, Hanover, Maryland). To account for interindividual variability, random effects were included in the model in an exponential relation: $\theta_i = \theta \times \exp(\eta_i)$, where θ_i is the parameter for individual i, θ the population parameter and η_i is the random difference between the population and individual parameter. In addition to the $COV step in NONMEM to determine the standard error of the (parameter) estimate, PsN's log likelihood profiling (llp) utility was used to determine the 95% confidence intervals of the for the C_{50} *RS*-ketamine, C_{100} *RS*-norketamine and $t_{1/2}k_{e0}$ parameters.

RESULTS

While all twenty subjects completed the experimental session without serious adverse events, data from three subjects were discarded because these subjects were unable to reliably score the ExP outcome. The mean age ± SD (range) of the remaining 17 subjects was 23 ± 2 (19-28) years, mean weight 82 ± 10 (60-98) kg, height (190 ± 6 (175-193) cm and body mass index 24 ± 2 (20-28) kg/m^2.

The initial model, including only an effect of *RS*-ketamine (absolute objective function (OVF) of 2,671 points) showed a clear underestimation of the ExP and PPT scores in the *RS*-ketamine infusion phase (data not shown). We therefore postulated a *RS*-norketamine effect for both outcomes. Expanding the initial model with *RS*-norketamine, improved the model by 157 OVF points. Since a potential hysteresis between the plasma *RS*-ketamine and *RS*-norketamine concentrations could not be excluded, effect compartments were added to the model. None of the tested covariates were included in the final model. Consequently, for the two endpoints, no differences in C50K, C100NK and k_{e0} could be detected (using one k_{e0} parameter for both compounds significantly improved the model by 42 OVF points). These data indicate that *RS*-ketamine and its metabolite *RS*-norketamine affect PPT and ExP with similar potencies and dynamics, suggestive of high dependency of the two measured endpoints.

Estimated pharmacodynamic parameter estimates are given in Table 1. Plots of the population predicted PPTs and ExP scores *versus* time, goodness of fit plots and a visual predictive check (VPC) based on 1000 simulated datasets are shown in Figures 1-3. All figures show that the model was able to adequately describe the pharmacodynamic data. Log Likelihood profiles (Fig. 4) for the for the C_{50} *RS*-ketamine, C_{100} *RS*-norketamine and $t_{1/2}k_{e0}$ parameters, showed 95% confidence intervals of 0.60-1.09 nmol/ml, 0.33-0.75 nmol/ml and 7.0-19.4 min respectively.

Table 1. Population Pharmacodynamic Parameter values.

	Typical parameter value (SEE) [%CV]	Inter-individual variability (%) (SEE) [%CV]
Baseline pressure pain threshold (N)	60.4 (6.04) [10]	40.4 (3.4) [13]
EMAX *External Perception* (mm)	100 FIX	106.8 (11.7) [11]
γ	4.59 (0.60) [13]	41.1 (8.6) [21]
C50 *RS*-ketamine (nmol/mL)	0.801 (0.192) [24]	-
C100 *RS*-norketamine (nmol/mL)	0.481 (0.154) [32]	25.8 (27.4) [36]
$t_{1/2}k_{e0}$ (min)	12.2 (3.9) [32]	46.9 (8.9) [19]
Additive error pressure pain threshold (N)	9.97 (2.2) [22]	-
Additive error external perception (mm)	5.9 (1.2) [22]	-

EMAX *External Perception* is the maximum possible effect of *External Perception*; γ is a shape parameter; C50 *RS*-ketamine is the estimated *RS*-ketamine concentration causing a 50% increase in pain pressure threshold and C100 *RS*-norketamine the *RS*-norketamine concentration causing a 100% increase in C50K; $t_{1/2}k_{e0}$ is theplasma effect compartment equilibrium half-life for both *RS*-ketamine and *RS*-norketamine.

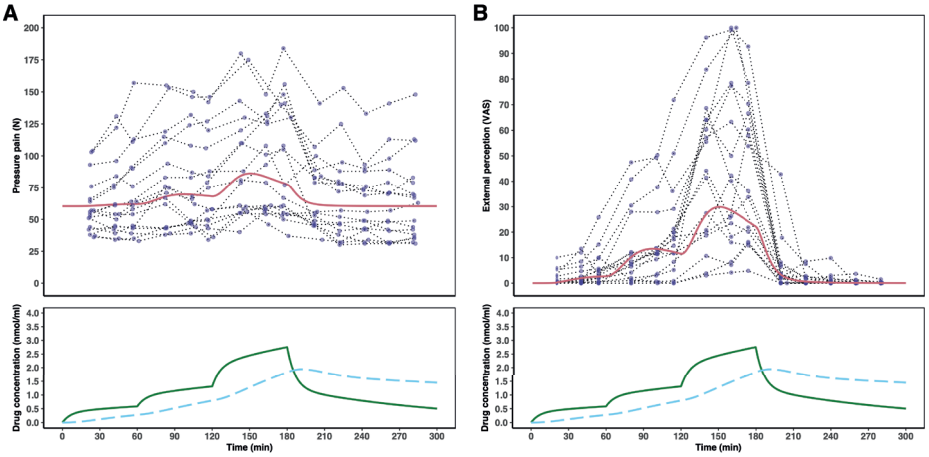

Figure 1. Plots showing the population predicted pharmacodynamic outcomes (red lines) and the observed datapoints for each individual *versus* time (dots and dotted lines) in the upper panels. (**A**) Plot showing pressure pain data and population predicted values and (**B**) plot showing external perception data and population predicted values. The lower two panels show the *RS*-ketamine (green line) and *RS*-norketamine (dashed blue line) concentration time profiles.

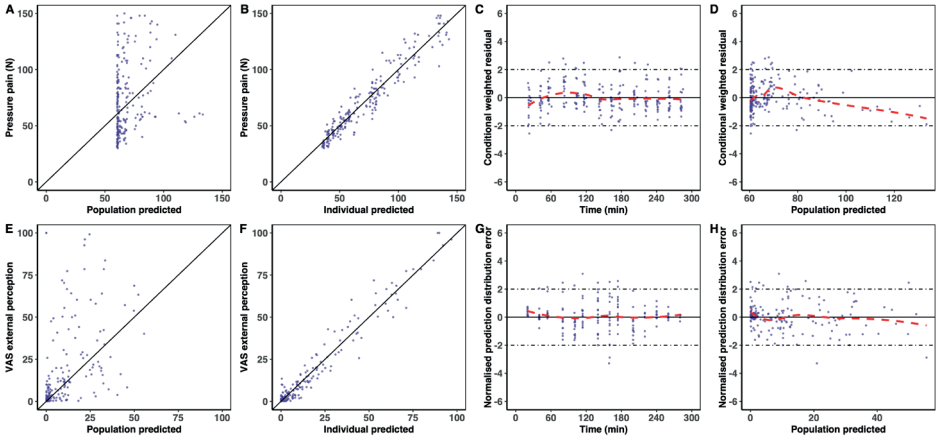

Figure 2. Goodness of fit plots for the population pharmacodynamic model. (**A-D**) Observed *versus* population predicted, observed *versus* individual predicted, conditional weighted residuals *versus* time and conditional weighted residuals *versus* population predicted plots for pressure pain. (**E-H**) Observed *versus* population predicted, observed versus individual predicted, conditional weighted residuals *versus* time and conditional weighted residuals *versus* population predicted plots for external perception.

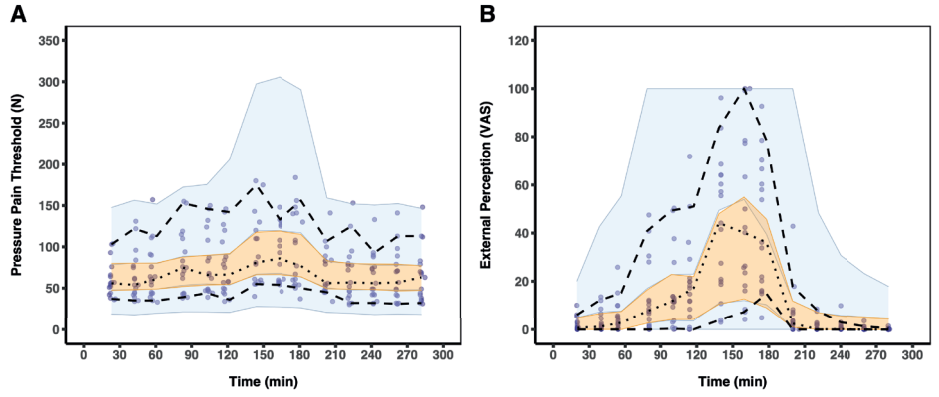

Figure 3. Visual predictive checks for the pressure pain threshold (**A**) and external perception (**B**) data. The middle dotted lines represent the 50th percentile of the observed data. The lower and upper dashed lines show the 5th and 95th percentiles of the observed data respectively. The 95% confidence interval for the 50th percentile of the simulated data is shown by the orange shaded area. The lower and upper gray shaded areas represent the 95% confidence intervals for the 5th and 95th percentiles of the simulated data.

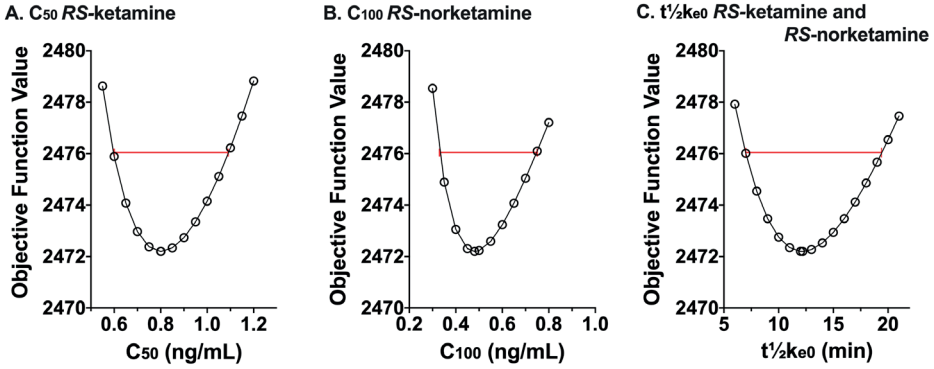

Figure 4. Log likelihood profiles for the C_{50} *RS*-ketamine (**A**), C_{100} *RS*-norketamine (**B**) and $t_{1/2}k_{e0}$ (**C**) parameters. The red bars show the final parameter 95% confidence interval as determined by PsN's "llp" utility.

DISCUSSION

We were unable to reject the Null hypothesis as our results show that *RS*-ketamine and *RS*-norketamine pharmacodynamics (*i.e.* potency and onset/offset times) were similar for endpoints pain pressure threshold and changes in external perception as a measure of ketamine dissociation. Since our results disagree with earlier findings,[6,7] it is important to discuss in detail the different items of our protocol that yielded the current results.

Pain test

We used a manual pressure pain device to detect the pain pressure threshold. Testing was done by a single experienced researcher who displayed a high reproducibility in obtaining the pain threshold response. Still, it may well be that different pain tests give different results with significant differences in pharmacodynamics. For example, in a previous study we tested the effect of the opioid alfentanil on noxious electrical and thermal stimuli and while the potency parameter was similar between tests, the value of the onset/offset parameter, $t_{½}k_{e0}$, differed significantly between tests.[15] We argued at the time that this indicates that the two tests are comparably potent under steady-state conditions but differ in their behavior under dynamic conditions. These differences in dynamic conditions were related to different neuronal circuits activated by the two tests. Hence, the outcome of the study may have been influenced by the choice of pain assay. This not only relates to our study but is equally relevant to other studies. Studying pain relief in chronic (neuropathic) pain patients may overcome this issue.

Dissociation

Dissociation was measured by the *External Perception* questions of the Bowdle questionnaire.[10] This questionnaire was developed in 1998 as a psychological inventory (a hallucinogen rating scale) to quantify ketamine-induced psychedelic symptoms in volunteers and has been used in multiple studies on the effect of various psychedelics on dissociative symptoms. Apart from the *External Perception*, the questionnaire encompasses Internal Perception and Drug High. To test the internal validity of our results, we additionally tested the other two measures of dissociation with similar results as with *External Perception* (data not shown). This indicates that our approach yielded a reliable effect-response relationship. Still, we cannot exclude that other measures of dissociation or other forms of parametrization might have given different results.

Participants

In our study healthy male volunteers were included. We restricted ourselves to a single sex so to prevent noise from possible sex differences. Sex differences have been observed in ketamine pharmacokinetics and pharmacodynamics. [16,17] For example, Morgan et al.[17] showed a greater decrease in cognitive performance in men compared to women following ketamine administration. Further studies are needed to determine the dependency of ketamine endpoints in mixed populations to determine a possible difference between the sexes. Additionally, it may well be that an even better model than the healthy and young volunteer is the patient (of either sex) with acute or chronic pain. Ketamine behavior as an analgesic (*i.e.* reducing existing pain) may well be different from its behavior as an antinociceptive agent (*i.e.* by subduing an experimentally induced pain response) due to differences in activated pain circuits in brain and spinal cord from these two distinct stimuli.

Pharmacodynamic modeling

We successfully modelled the two endpoints simultaneously in our pharmacodynamic analysis. An interesting observation in our data is that PPT and ExP tended to decrease before the *RS*-ketamine infusion ended (Fig. 1). We reasoned that this might be related to the slow but steady increase in concentration of one of ketamine's metabolites. Addition of a norketamine component to the model improved the data fits significantly. This agrees with earlier findings in which norketamine had an antagonistic effect on ketamine-induced pain relief and neurocognitive impairment.[14] Whether this is related to the competition for binding locations on the *N*-methyl-D-aspartate (NMDA) receptor and assuming that norketamine has no inherent efficacy at the receptor, or is related to an effect of norketamine at other receptor systems remain unknown. We tend to the latter hypothesis as studies in rodents show that norketamine has analgesic properties.[18]

The covariate analysis detected no differences between endpoints with respect to potency parameter C50. This indicates that the pain relief and external perception behaved similarly in the steady state. Parameterization of the pharmacodynamic models with distinct C50 values for PPT and ExP gave similar results (data not shown). The values of ketamine C50 depend on the parametrization of the pharmacodynamic models. Apparently, the C50 for ExP matches the C50 for Antinociception, considering the fact that the power function of PPT is an inverse sigmoid.[12] Additionally, the dynamic properties of the PPT and ExP responses were similar with the need for only one parameter for the equilibration between plasma and postulated effect-site concentration (k_{e0}); a model without effect compartment was inferior to the model with just one k_{e0}. Since ketamine displays rapid receptor kinetics,[19] the hysteresis in response ($t_{1/2}k_{e0}$ = 12.2 ± 3.9 min) is best explained by the transfer of ketamine from plasma to its sites of action within the central nervous system and neuronal dynamics.

CONCLUSIONS

We reasoned that similar values for potency (C50 and C100) and $t_{1/2}k_{e0}$ indicate a close and possibly even mechanistic association between endpoints, in agreement with earlier statements that ketamine analgesia is intricately bound to its dissociative effects.[3] Still, this reasoning stands in contrast to earlier observations.[6,7] Gitlin et al.[6] used a statistical approach to show that ketamine and carefully state that ketamine's analgesic effects are not *exclusively* caused by dissociation. Jonkman et al.[7] studied nitric oxide (NO) donation during *S*-ketamine and *RS*-ketamine infusion and concluded that NO depletion following blockade of the NMDA receptor is associated with the psychedelic effects induced by ketamine. The theory behind this observation is that reduced intraneural levels of NO lead to reduction in neuroprotection, neuroplasticity and neurotrophic conditions. Adding NO restores these protective effects and ameliorates psychedelic experience. Interestingly, NO donation had an effect on racemic ketamine but not *S*-ketamine induced psychedelic effect. This suggests that *S*-ketamine induces its psychedelic effect *via* a NO-independent pathway. We did try to unravel the pharmacodynamics of *R*- and *S*-isomers in our study but failed to do so (data not shown). It may well be that the *R*- and *S*-isomers act differently but we could not discriminate between pathways that would suggest dependency or independency between dissociation and analgesia. Such differences may be expected given the different potencies of *R*- and *S*-ketamine in inducing slowing of the electroencephalogram.[20]

Given the complexities of our study and data analysis, *i.e.* complexities related to the pain model, measurement of dissociation, participants and complex modeling of the combination of *RS*-ketamine and *RS*-norketamine, we conclude that although our data

support an intricate association between ketamine analgesia and dissociation, we cannot exclude that some (small) part of the analgesic effects of ketamine is independent from its dissociative effects. In this respect we agree with Gitlin et al.[6]

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General Discussion and Conclusions

In this thesis, the focus was on the study of the pharmacodynamics and pharmacokinetics of ketamine. To start with, we synthesized an update on a previously published review[1] from our department on the newest developments in the field of ketamine therapy for neuropathic pain in **Chapter 2**. Neuropathic pain is a condition that is, in general, difficult to treat, with a treatment effect in only 30-60% of the cases. Although neuropathic pain is defined by the IASP as "pain caused by a lesion of the somatosensory nervous system",[2] neuropathic pain is mainly a description of a condition, rather than a disease that can clearly be diagnosed by the detection of lesions. In fact, in many cases of neuropathic pain, the etiology of the disease remains unknown.

Several of the most interesting new developments in the field of ketamine treatment are the new investigations into inhaled ketamine and the upcoming of intra-nasal ketamine for procedural sedation in children.[3] Furthermore, a new intra-nasal ketamine has been approved by the FDA and EMA for the treatment of treatment-resistant depression.[4] These new administration routes might enable the safe an easy use of ketamine outside the clinic, without the need of intravenous access.

Furthermore, we searched the literature for systematic reviews, published since 2012, assessing randomized clinical trials that evaluated the efficacy of ketamine therapy for the treatment of neuropathic pain. Five reviews and meta-analyses were obtained reporting on the effect of ketamine for the treatment of chronic neuropathic pain.[5-9] Two additional reviews evaluating ketamine treatment for cancer pain were included, since cancer pain often is a combination of nociceptive and neuropathic pain.[10,11] In the 2012 review, it was stated that definitive evidence for the efficacy of ketamine for neuropathic pain was limited, due to a lack of adequate randomized clinical trials.[1] We stated that, as in 2012, good-quality RCTs showing the definitive evidence for the efficacy of ketamine for the treatment of neuropathic pain are still lacking. However, it was possible to elude certain trends from the selected meta-analyses and reviews: (i) current data suggests that i.v ketamine shows superior analgesic efficacy compared to other administration forms, (ii) the effect of i.v. ketamine is limited and often of relatively short duration, (iii) longer infusion durations were associated with longer lasting effects and (iv) most studies did not focus on a specific type of neuropathic pain (*e.g.* patients with central sensitization), but mostly on neuropathic pain patients in general.

Finally, we found one animal study that showed promising results with (2*R*,6*R*)-hydroxynorketamine in three different mouse models for pain, including neuropathic pain.[12] The (2*R*,6*R*)-hydroxynorketamine showed to be superior to ketamine when it comes to producing long-lasting relief of allodynia, which is likely to be caused by its neurotrophic and neuroplastic effects. Moreover, mice treated with (2*R*,6*R*)-hydroxynorketamine showed significantly fewer side effects compared the animals treated with ketamine.

Ketamine pharmacokinetics are studied in a wide variety of study designs, study populations and administrations forms. In **Chapter 3**, we set out to combine the data of several of these studies into one single ketamine population pharmacokinetic model. First, a systematic literature search was performed for pharmacokinetic modeling studies with ketamine in human subjects. Literature searches resulted in 30 studies that used a pharmacokinetic modeling approach to describe ketamine pharmacokinetics. To come to an overall view of ketamine pharmacokinetics, we performed three different analyses with the data that were obtained from the included studies: (i) the calculation of the mean weighted Vd (volume of distribution) and CL (clearance) parameters, (ii) the development of a meta-analytical three compartment model and (iii) the development of a five compartment pharmacokinetic model based on 14 raw data sets, shared by the original authors. In addition, potential effects of study population characteristics (*e.g.* adult *versus* pediatric and healthy *versus* patients), ketamine administration form, ketamine enantiomer measured and venous *versus* arterial sampling were tested. No significant effects were found on the mean weighted Vd and CL parameters, calculated in the meta-analysis. However, raw data analysis showed an effect of the ketamine enantiomer on the elimination clearance.

In general, non-linear mixed effect modelling might be considered to be the golden standard when it comes to the analysis of pharmacokinetic data, partially because it is not only able to describe population parameters, but also because it is able to show how these population parameters vary among the population. However, despite its advantages, raw data analysis can be a cumbersome process and, as shown in Chapter 3, it is often difficult to retrieve raw datasets from all relevant studies. On the contrary, the meta-analytical approach might not allow description of the parameter variability, although this problem might be partially solved by incorporating inter-study parameter variability. More importantly, the meta-analytical approach is a much less time consuming process, needing substantially less computing power when compared to the raw data analysis. Finally, since modelling data that are presented in the original papers is sufficient to develop a meta-analytical pharmacokinetic model, the availability of the data is not an issue when using this approach.

Simulations of a clinically plausible dosing regimen of the three-compartment meta-analytical model and the raw-data model showed only minor differences in the concentration-time profiles between these two approaches, with the concentrations of the meta-analytical model typically lying between the venous and arterial concentrations of the raw data model. These findings further suggest that the meta-analytical approach might be an interesting option in cases where (i) it is hard if not impossible to retrieve raw data for all included studies, (ii) parameter, and hence simulated concentration variability, is of lesser importance for the application of the modeling study, (iii)

only limited computing resources are available and (iv) time available to perform the analysis is limited.

When including the mode of sampling as a covariate, no significant effect was found on either Vd or CL in the meta-analytical approach. However, evaluation of the context sensitive half-time (*i.e.* elimination half-times after different infusion durations), revealed substantial differences for models that were based on either venous or arterial sampling. The difference between venous and arterial context sensitive half-times increased with longer infusion durations, with substantially longer context sensitive half-times for the venous models.

Including two arterial delay compartments to describe venous concentrations resulted in a significant improvement of the raw data model. As shown in the simulations (Fig. 8), after a 40 min infusion of 0.5 mg/kg ketamine, arterial concentrations were higher during the infusion phase. However, after ceasing the infusion, arterial concentrations decreased more rapidly than venous concentrations, resulting in higher venous plasma concentrations compared to the arterial plasma concentrations.

When simulating longer infusion durations, up to 7 h (data not shown in his thesis) venous and arterial steady state concentrations showed to be similar. This suggests that venous-arterial differences in pharmacokinetics are mainly relevant when considering i.v. bolus administrations or short infusions and less relevant when studying pharmacokinetics after a continuous infusion regimen. Moreover, when using a pharmacokinetic analysis for further pharmacodynamic studies, one should be aware of the therapeutic window of the study drugs: for drugs with a wide therapeutic window, concentration differences between different modes of sampling might be clinically irrelevant. On the contrary, when studying drugs with a narrow therapeutic window, differences in plasma concentrations between venous and arterial sampling could become clinically relevant.

Although a plethora of models describing ketamine pharmacokinetics have been published, relatively little is known about the pharmacokinetics of its metabolites, with hydroxynorketamine and dehydronorketamine in particular. In **Chapter 4**, a seven compartment model was developed to describe the pharmacokinetics of ketamine, norketamine, dehydronorketamine and hydroxynorketamine data obtained from a randomized double blinded crossover study in 20 healthy male volunteers. The subjects received escalating i.v. infusions of either *S*- or *RS*-ketamine in combination with either placebo or sodium nitroprusside (SNP) during four different study visits. At each of the study visits, blood samples were acquired during 300 minutes and plasma concentrations of ketamine and its metabolites were determined.

After ceasing the ketamine infusion (t = 180 min), ketamine plasma concentrations rapidly declined. However, substantial plasma concentrations of the metabolites were still observed at the end (t = 300 min) of the sampling scheme. This is an important finding, since the analgesic effects of ketamine for specific types of neuropathic pain

are still observed after the ketamine concentrations decreased.[13] As mentioned above, studies showed significant analgesic effects of the (2*R*,6*R*)-hydroxynorketamine metabolite in a murine model for neuropathic pain.[12]

Clear differences were found between the clearances of the *S*- and *R*-enantiomers of ketamine and its metabolites. Our study showed elimination clearances up to 50% lower for all *R*-enantiomers compared to their *S*-enantiomer counterparts. Although several studies reported lower elimination clearances for *R*-ketamine compared to *S*-ketamine, it was unknown whether this effect would also be observed for the (secondary) metabolites.[14-17] To our knowledge, only one pharmacokinetic model including stereo-specific dehydronorketamine and total hydroxynorketamine has been currently been published. However, this study from Zhao et al.[18] only included 9 patients who were only scarcely sampled. Therefore, interpretation of their model should be done cautiously, since the limited number of samples, especially in the metabolite formation phase, might be insufficient to reliably estimate the formation rates of the metabolites. On the other hand, because sampled up to 3 days post-dose, Zhao et al. were able to show the presence of significant dehydronorketamine and hydroxynorketamine concentrations up to one day after ketamine administration.

SNP was administered to evaluate its potential mitigating effect on the side effects caused by ketamine administration.[19] However, simulations showed that SNP did not cause any major, and clinically relevant differences in ketamine and metabolite pharmacokinetics. This supports the hypothesis that the mitigating effect op SNP on ketamine side effects is caused by a change in pharmacodynamics, and not by a change in pharmacokinetics.[19]

In retrospect, the sampling duration was too short to fully describe the pharmacokinetics of dehydronorketamine and hydroxynorketamine, likely due to the lack of sampling points in the elimination phases of the secondary metabolites. However, the final model was of sufficient quality to be used for the pharmacodynamic modeling studies.

In **Chapter 5** we elaborate further on the study described in Chapter 4 and by Jonkman et al.[19] In this chapter, the relation between ketamine (and metabolite) plasma concentrations and the effect on cardiac output was studied.

Differences in potency between *S*- and *R*-ketamine have been reported for several pharmacodynamic outcomes.[20-22] In our study, the addition of an *R*-ketamine effect did not lead to a significant improvement of the model, suggesting that *S*- and *R*-ketamine have a differential sympathoexcitatory effect. This difference might be explained by (i) a lower binding affinity of *R*-ketamine for the target receptors and (ii) a lower activity of *R*-ketamine once it is bound to the target receptors.

Raw cardiac output data showed a clear undershoot after termination of the ketamine infusion. We therefore initially included a controller mechanism in our model, as published previously.[23] This controller counteracts the initial increase in cardiac

output caused by ketamine, eventually returning the cardiac output to baseline. However, without the initial controller mechanism, we found a significant, though negative, contribution of *S*-norketamine on the cardio-excitatory effect induced by *S*-ketamine. This observation is in line with the results from a previous modeling study, where norketamine counteracted the analgesic effect of ketamine.[24]

Earlier studies indicated that SNP co-administration could reduce the psychedelic side effects of ketamine.[19,25] However, our analysis failed to show a similar mitigating effect on the cardiac side effects caused by ketamine. We postulated that this finding might be caused by compensatory mechanisms in our young and healthy male study population. Moreover, we reasoned that the SNP dose used during the experiments might have been too low to reduce the increase in cardiac output.

Finally, in **Chapter 6**, we performed a population pharmacodynamic modeling sub-analysis of the study previously published by Jonkman et al.[19] A recent study in 15 healthy volunteers, suggested that the analgesic effects observed after racemic ketamine administration are independent from the dissociative effects.[26] We therefore used a population pharmacodynamic modeling approach for the analysis of pressure pain threshold and external perception data from the study occasion where racemic ketamine was administered in combination with placebo. To support the findings of Gitlin et al. [26] we hypothesized that pressure pain and external perception were independent.

First, we found no differences in the potency parameter (C50 parameter) between the two endpoints. Although this indicates that the two endpoints showed similar behavior in the steady state, one should be careful to draw the conclusion that pressure pain and external perception are dependent, since the C50 parameter also depends on the parameterization of the pharmacodynamic models. Moreover, the model with a single plasma-effect site equilibration parameter (k_{e0}) best described the data, suggesting similar dynamics of the pressure pain and external perception responses.

Although our analysis was unable to show clear evidence that the analgesic effects were independent from the psychedelic/dissociative effects, we cannot fully exclude that at least some part of the analgesic effect is independent from the dissociative effects. In our study, a pressure pain threshold test was used, whereas Gitlin et al. used a cuff pain test to score pain outcomes. Different neuronal signaling pathways may be involved in different pain types, so that the dependence between analgesia and dissociation might vary among different types of pain. The same might be true for the evaluation of the dissociative effects, since different tests are used to rate the dissociative effects. These differences further complicate direct comparison between studies.

FUTURE PERSPECTIVES

Since adequate RTCs evaluating the efficacy of i.v. ketamine for the treatment of neuropathic pain are lacking, new RCT data are needed to come to a definite conclusion. However, up to now, these RCTs made no distinction between the different types/etiologies of neuropathic pain in their study populations. Since overexpression of ketamine's main target receptor, NMDAR is associated with central sensitization, studying patients with central sensitization *versus* patients without central sensitization might be one step further in solving the puzzle. Moreover, considering the promising results with experimental (2*R*,6*R*)-hydroxynorketamine treatments in mice, the possibility of (2*R*,6*R*)-hydroxynorketamine as an analgesic agent in humans should we further explored. However, further research in this direction might be challenging since currently no (2*R*,6*R*)-hydroxynorketamine is available for human use.

In the meta-analysis, we were only able to test for a limited number of potential covariate effects. Due to the extremely heterogeneous data, effects such as autoinhibition after bolus *versus* continuous infusions, the effects of specific types of disease states or the role of pharmacogenetics on ketamine pharmacokinetic behavior could not be tested. Improvement of the quality of the data that is available for modeling purposes, would greatly aid further model development. Moreover, the current model could be validated with external datasets, for potential applications in targeted controlled infusion systems.

Due to (i) the relatively short sampling scheme and (ii) the inability to directly administer the ketamine metabolites to our subjects, metabolic fractions (*e.g.* the fractions of each parent compound that are converted to the different metabolites) and central metabolite compartment volumes could not be estimated. Moreover, due to the relatively short sampling regimen, data points in the dehydronorketamine and hydroxynorketamine elimination phases were scarce, further adding to the problem. New studies into ketamine and metabolite pharmacokinetics may use longer sampling schemes (*e.g.* up to 24-48h post dose) to tackle this problem. In addition, collecting urine samples may give additional information about the ketamine fractions that are converted to norketamine and subsequently to either dehydronorketamine or hydroxynorketamine.

In this thesis, the relation between psychedelic effects and analgesia was evaluated by using pressure pain threshold data. However, in clinical practice, ketamine might be used for the treatment of neuropathic pain syndromes, in which different neuronal pain circuits are involved. Translation of the current experimental study in healthy volunteers to the situation in the clinic might therefore be challenging. New studies on the relation between ketamine analgesic and dissociative effects in neuropathic pain patients are therefore warranted.

CONCLUSIONS

Considering the data and analyses performed in this thesis, it can be concluded that:

1. Decent quality RCTs showing the definitive proof for the efficacy of ketamine for the treatment of neuropathic pain are still scarce.
2. Pharmacokinetic outputs from the meta-analytical model and raw data model were similar.
3. After an initial decrease in ketamine concentrations, significant (secondary) metabolite concentrations are observed up to at least two hours after termination of the ketamine infusion.
4. The mitigating effect of SNP on the psychedelic side effects is unlikely to be driven by pharmacokinetic mechanisms.
5. The potency of *S*-ketamine to induce an increase in cardiac output is significantly higher than that of *R*-ketamine.
6. Our analyses cannot fully exclude that at least some part of the analgesic effects of ketamine are independent from the psychedelic effects.

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8

Nederlandse Samenvatting

In dit proefschrift hebben we de farmacokinetiek en farmacodynamiek van ketamine onderzocht. Als eerste zijn we in **Hoofdstuk 2** begonnen met een update van een review, welke voorheen gepubliceerd is door onze onderzoeksgroep.[1] Er is gekeken naar de meest recente ontwikkelingen betreffende het gebruik van ketamine bij neuropathische pijn. Neuropathische pijn is een aandoening die over het algemeen lastig te behandelen is: behandeling heeft bij slechts 30-60% van de gevallen een effect. Hoewel de IASP neuropathische pijn definieert als "pijn veroorzaakt door laesies in het somatosensorische zenuwstelsel",[2] is neuropathische pijn vooral een beschrijving van een aandoening en in mindere mate een aandoening die duidelijk gediagnostiseerd kan worden door het aantonen laesies. De etiologie van aandoeningen welke neuropathische pijn veroorzaken, is dan ook in veel gevallen onbekend.

Een aantal van de meest opzienbarende ontwikkelingen op het gebied van ketaminebehandeling zijn studies betreffende inhalatie- en intranasaal ketamine en het voor procedurele sedatie in kinderen.[3] Bovendien is er recentelijk een nieuwe intranasale variant van ketamine door de FDA en EMA goedgekeurd voor de behandeling van therapieresistente depressie.[4] Een groot voordeel van deze nieuwe toedieningswegen is dat ze er toe kunnen leiden dat het eenvoudiger wordt ketamine veilig toe te dienen. Hierdoor wordt het gemakkelijker om ketamine buiten de kliniek te gebruiken.

Vanuit bovenstaande inzichten hebben we in de bestaande literatuur gezocht naar systematische reviews die na 2012 gepubliceerd zijn en waarbij er specifiek is gekeken naar gerandomiseerde klinische studies (RCTs) die de effectiviteit onderzochten van ketamine bij de behandeling van neuropathische pijn. In totaal vonden we vijf geschikte reviews en meta-analyses.[5-9] Daarnaast hebben we nog twee extra reviews geïncludeerd, waarin de effectiviteit van ketamine bij de behandeling van oncologische pijn werd geëvalueerd, aangezien dit soort pijn vaak een combinatie is tussen nociceptieve en neuropathische pijn.[10,11] In de review uit 2012 werd geconcludeerd dat definitief bewijs voor de effectiviteit van ketamine bij de behandeling voor neuropathische pijn beperkt was door een gebrek aan goede RCTs.[1] Net als in 2012, concluderen wij ook nu dat goede RCTs, waarbij de effectiviteit van ketamine bij neuropathische pijn wordt bestudeerd, ook op dit moment nog erg schaars zijn. Echter was het wel mogelijk om een aantal voorzichtige trends waar te nemen: (i) de huidige data suggereren dat de i.v. toediening van ketamine een beter analgetisch effect geeft dan andere toedieningsvormen; (ii) het effect van i.v. ketamine is slechts gering en het effect houdt vaak relatief kort aan; (iii) de duur van ketamine infusie speelt een rol in hoe lang het effect na infusie aanhoudt en (iv) dat de meeste studies neuropathische pijn in het algemeen beschouwen en niet focussen op een specifiek type neuropathische pijn, zoals patiënten met centrale sensitisatie.

Als laatste vonden we een dierstudie waarbij veelbelovende resultaten werden gerapporteerd met (2*R*,6*R*)-hydroxynorketamine in drie verschillende muis model-

len voor (neuropathische) pijn.[12] De (2*R*,6*R*)-hydroxynorketamine liet bij deze studie een aanzienlijk sterker en langer durend effect zien op allodynie in vergelijking met ketamine, hetgeen mogelijk veroorzaakt wordt door neurotrope en neuroplastische effecten. Bovendien ondervonden de muizen die met (2*R*,6*R*)-hydroxynorketamine werden behandeld significant minder bijwerkingen dan de dieren die met ketamine behandeld waren.

De farmacokinetiek van ketamine is reeds uitbundig bestudeerd in meerdere, maar uiteenlopende studies, studie populaties en toedieningsvormen. Om deze uiteenlopende data te combineren, wilden we in **Hoofdstuk 3** één model maken om de farmacokinetiek van ketamine in verschillende (patiënt) groepen te beschrijven. Als eerste is er systematisch in de literatuur gezocht naar studies waarbij farmacokinetische modellen werden beschreven die waren gebaseerd op data in mensen. De zoekopdrachten resulteerden in 30 studies die farmacokinetische modellen rapporteerden voor het beschrijven van de farmacokinetiek van ketamine. Om een algemeen beeld te schetsen van de farmacokinetiek van ketamine, hebben we in hoofdstuk 3 drie verschillende analyses uitgevoerd met de data uit de geïncludeerde studies: (i) de berekening van de gewogen gemiddelde Vd (verdelingsvolume) en CL (eliminatie klaring) parameters; (ii) het ontwikkelen van een meta-analytisch 3 compartimenteel model en (iii) het ontwikkelen van een 5 compartimenteel populatie farmacokinetisch model dat was gebaseerd op 14 ruwe datasets, welke met ons gedeeld waren door de originele auteurs. Daarnaast hebben we gekeken naar de potentiele effecten van de eigenschappen van de studiepopulaties (bijv. volwassenen *versus* kinderen, gezonde subjects *versus* patiënten), de gebruikte ketamine toedieningsvorm, het gemeten ketamine enantiomeer en of er veneus of arterieel was bemonsterd. Geen van bovenstaande eigenschappen gaf een significant effect op het meta-analytische model. Echter, bij de ruwe data-analyse vonden we een significant effect van het type ketamine enantiomeer dat was gemeten op de eliminatie klaring.

In het algemeen wordt aangenomen dat *non-lineair mixed effect modelling* de gouden standaard is voor het analyseren van farmacokinetische data. Niet alleen voor het schatten van populatieparameters, maar met name vanwege het vermogen om te beschrijven hoe deze parameters variëren binnen en tussen populaties. Afgezien van feit dat het een krachtige methode is voor het analyseren van dergelijke data, is het een complexe methode en kan het in de praktijk erg lastig zijn om alle relevante ruwe data te verkrijgen, zoals Hoofdstuk 3 laat zien. De meta-analytische methodiek is minder geschikt voor het bepalen van de parameter variabiliteit, echter zou dit probleem deels opgelost kunnen worden door het bepalen van de inter-studie parameter variabiliteit. Aan de andere kant heeft de meta-analytische methode het voordeel dat het relatief snel en eenvoudig uitgevoerd kan worden en dat het aanzienlijk minder rekenkracht nodig heeft in vergelijking met *non-linear mixed effect modeling*. Bovendien kan er bij

de meta-analytische methode gemakkelijk gebruik worden gemaakt van de parameters die gerapporteerd zijn in de geïncludeerde studies; de beschikbaarheid van de ruwe data is hierbij dus minder een probleem vergeleken met de ruwe data-analyse.

Simulaties van klinisch plausibele doseringsschema's gebaseerd op het drie compartimentele meta-analytische model en het ruwe data model, lieten tussen deze twee modellen slechts geringe verschillen in concentratie-tijd profielen zien. De concentratie-tijd profielen van het meta-analytisch model lagen hierbij meestal tussen de gesimuleerde veneuze en arteriële concentraties van het ruwe-data model. Deze bevindingen suggereren dat de meta-analytische methode mogelijk een interessante optie is voor specifieke gevallen waarbij (i) het moeilijk of onmogelijk is om voldoende ruwe data te verkrijgen voor een ruwe data-analyse; (ii) parameter, en uiteindelijk dus ook concentratie, variabiliteit minder relevant is voor de vraagstelling van de studie; (iii) er slechts beperkte rekencapaciteit beschikbaar is en (iv) wanneer een analyse snel uitgevoerd dient te worden.

De arterieel *versus* veneuze bemonstering liet geen significant effect zien op Vd of CL bij de meta-analytische methode. Echter lieten de context sensitieve half-waarde tijden (eliminatie half-waarde tijdens na verschillend durende infusies), aanzienlijke verschillen zien tussen de modellen die op veneuze en arteriële data gebaseerd waren. Hierbij werd het verschil in context sensitieve half-waarde tijden tussen veneuze en arteriële modellen groter naarmate de duur van de gesimuleerde infusies toe nam, met langere context sensitieve half-waarde tijden voor de veneuze modellen.

Het includeren van twee arteriële *delay* compartimenten voor het beschrijven van de veneuze data, gaf dan ook een significante verbetering van het ruwe data model. Zoals te zien is in de simulaties (Fig. 8) in hoofdstuk 3, waren de arteriële concentraties hoger dan veneuze concentraties tijdens een 40 min durende infusie met 0.5 mg/kg ketamine. Desalniettemin namen de arteriële concentraties sneller af dan de veneuze concentraties nadat de infusie gestopt was, waardoor de veneuze concentraties uiteindelijk hoger werden dan de arteriële concentraties. Dit liet duidelijk zien dat de veneuze concentraties na-ijlen op de arteriële concentraties.

Wanneer er infusies korter dan 7 uur gesimuleerd worden, zijn de veneuze en arteriële steady-state concentraties nagenoeg gelijk. Dit suggereert dat veno-arteriële verschillen in farmacokinetiek vooral relevant zijn bij korte infusies of bij i.v. bolus toediening en minder relevant wanneer er gekeken wordt naar de farmacokinetiek bij langdurige infusieprotocollen. Bovendien hangt de klinische relevantie van eventuele veno-arteriële concentratieverschillen ook af van het therapeutisch venster van het geneesmiddel in kwestie: voor geneesmiddelen met een breed therapeutisch venster zullen de relatief kleine verschillen tussen arteriële en veneuze concentraties niet of minder relevant zijn, terwijl deze kleine concentratieverschillen misschien wel klinisch relevant kunnen zijn voor geneesmiddelen met een smal therapeutisch venster.

Er is een aanzienlijk aantal farmacokinetische modellen gepubliceerd voor ketamine. Desondanks is er tot op heden weinig bekend over de farmacokinetiek van de gevormde metabolieten en in het bijzonder die van hydroxynorketamine en dehydronorketamine. In **Hoofstuk 4** wordt daarom een studie beschreven waarin een zeven compartimenteel model wordt ontwikkeld dat de farmacokinetiek van ketamine, norketamine, hydroxynorketamine en dehydronorketamine beschrijft in 20 gezonde vrijwilligers in een gerandomiseerde dubbel blinde klinische studie. In deze studie kregen de proefpersonen toenemende i.v. infusies van *S*- of *RS*-ketamine in combinatie met een placebo of natrium nitroprusside, tijdens vier verschillende studie momenten. Tijdens de experimenten werden op verschillende momenten bloedmonsters afgenomen gedurende 300 minuten, waarna de plasmaconcentraties van ketamine en bovengenoemde metabolieten werden bepaald.

Nadat de ketamine infusie gestopt was (t = 180 min), namen de plasmaconcentraties van ketamine snel af. Daarentegen waren er aan het eind van elke meting (t = 300 min) nog aanzienlijke metaboliet concentraties te zien. Dit is een belangrijke waarneming, aangezien het analgetische effect van ketamine in specifieke types neuropathische pijn nog enige tijd aan kan houden, terwijl de ketamine concentraties af zijn genomen.[13] Zoals eerder vermeld, is er bewijs voor de analgetische werking van (2*R*,6*R*)-hydroxynorketamine in muis modellen voor neuropathische pijn.

De analyses lieten een wezenlijk verschil zien tussen de eliminatie klaringen van de *S*- en *R*- enantiomeren van ketamine en metabolieten. Onze resultaten lieten tot 50% lagere eliminatie klaringen zien voor *R*-enantiomeren in vergelijking tot *S*-ketamine. Hoewel een aantal studies reeds rapporteerden over mogelijk lagere eliminatie klaringen voor *R*-ketamine in vergelijking met *S*-ketamine, was het nog onbekend of dit verschil ook zou worden gezien bij de eliminatie klaringen van de metabolieten.[14-17] Voor zover ons bekend is, is er tot op heden slechts één ander farmacokinetisch model gepubliceerd waarbij norketamine en dehydronorketamine stereospecifiek gemeten en geanalyseerd zijn.[18] Echter includeerde deze studie van Zhao et al. slechts 9 patiënten en was het aantal monsters per patiënt zeer gering. Het is daarom lastig harde conclusies te trekken uit hun resultaten, gezien het zeer beperkte aantal monsters (ook in de fase waarin metabolieten gevormd worden), waardoor de snelheden waarmee de metabolieten gevormd werden waarschijnlijk niet goed geschat konden worden. Daarentegen hebben Zhao et al. tot drie dagen na de ketamine gift bloedmonsters afgenomen, waardoor ze aan hebben kunnen tonen dat er nog significante concentraties dehydronorketamine en hydroxynorketamine aanwezig zijn tot minstens 1 dag na de ketamine toediening.

Natrium nitroprusside werd tijdens onze experimenten samen met ketamine toegediend, om te kijken of het een eventuele verlichting van de psychedelische bijwerkingen van ketamine kon geven.[19] Simulaties met ons farmacokinetisch model lieten

echter zien dat het effect van natrium nitroprusside op de farmacokinetiek gering is. Deze bevinding ondersteunt de hypothese dat het verlichtende effect van natrium nitroprusside op de psychedelische bijwerkingen met name veroorzaakt wordt door een farmacodynamisch mechanisme en niet doordat het de farmacokinetiek van ketamine en metabolieten verandert.

Terugkijkend op de experimenten kunnen we stellen dat er te kort bemonsterd is om de farmacokinetiek van dehydronorketamine en hydroxynorketamine volledig te kunnen beschrijven. Dit heeft waarschijnlijk te maken met het feit dat er niet tot nauwelijks bemonsterd is in de eliminatie fase van deze secundaire metabolieten. Desondanks kon wel geconcludeerd worden dat het finale model de farmacokinetiek goed genoeg beschreef om gebruikt te worden voor verdere farmacodynamische modelleringsstudies.

In **Hoofdstuk 5** gaan we verder met data uit de studie zoals gepubliceerd door Jonkman et al. In dit hoofdstuk wordt er gekeken naar de relatie tussen ketamine en metaboliet plasma concentraties en het effect op de cardiac output.

Verschillen tussen *S*- en *R*-ketamine in de mate waarop zij tot verscheidene farmacodynamische effecten leiden zijn gemeld in meerdere studies.[20-22] De toevoeging van een *R*-ketamine effect liet geen significante verbetering zien van ons model. Dit suggereert dat *S*- en *R*-ketamine verschillen in de mate waarop zij sympatico excitatie veroorzaken. Dit verschil kan mogelijk worden uitgelegd door (i) een lagere bindingsaffiniteit van *R*-ketamine voor de *target* receptoren en (ii) een minder sterke werking op de receptoren in vergelijking met *S*-ketamine.

De ruwe cardiac output data lieten een duidelijke trend zien waarbij, na het stoppen van de ketamine infusie, de *cardiac output* eerst kortdurend onder de baseline waarde schoot, alvorens zich te herstellen naar de baseline *cardiac output* waarde. Voor deze zogenaamde "undershoot" in de data, is er initieel een controller mechanisme in het model opgenomen, welke het initieel toenemend effect van ketamine op de cardiac output tegenwerkt.[23] In de modellen zonder een controller mechanisme, vonden we echter een significant, maar tegenwerkend effect van *S*-noketamine op het cardio excitatoire effect van *S*-ketamine. Deze bevinding is in overeenstemming met de resultaten uit een vorige modelling studie, waarbij norketamine het analgetische effect van ketamine bleek tegen te werken.[24]

Eerdere studies suggereerden dat gelijktijdige toediening van natrium nitroprusside de psychedelische bijwerkingen van ketamine kon verminderen.[19,25] Uit de huidige analyse blijkt dat natrium nitroprusside geen effect heeft op de cardiovasculaire bijwerkingen van ketamine. Mogelijk kan dit verklaard worden door (cardiovasculaire) compensatoire mechanismen in onze jonge gezonde studie populatie en/of doordat de gebruikte dosis natrium nitroprusside te laag was om het effect van ketamine op het cardiovasculaire systeem tegen te gaan.

Als laatste hebben we een sub-analyse uitgevoerd van de data uit de studie zoals gepubliceerd door Jonkman et al.[19] In een recentelijk gepubliceerde studie met 15 gezonde vrijwilligers, rapporteerde Gitlin et al. dat het analgetische effect van *RS*-ketamine onafhankelijk was van de dissociatieve effecten.[26] **Hoofdstuk 6** betreft een farmacodynamische modellering studie, waarbij we specifiek gekeken hebben naar de drukpijn *threshold* en externe perceptie, tijdens en na toediening van *RS*-ketamine. Om deze stelling, zoals ingenomen door Gitlin et al., te ondersteunen, was onze hypothese dat de eindpunten drukpijn en externe perceptie onafhankelijk van elkaar zouden zijn.

Ten eerste lieten onze analyses geen significant verschil zien tussen de potentie parameters (C50 parameter) tussen de twee eindpunten. Hoewel dit suggereert dat de beide eindpunten vergelijkbaar gedrag vertonen in de *steady state*, kan hieruit niet *per se* geconcludeerd worden dat drukpijn en externe perceptie afhankelijk van elkaar zijn. Dit komt met name doordat de waarde van de C50 parameter ook voor een groot deel afhangt van de parametrisering van de modellen. Ten tweede was het model met slechts één plasma-*effect side* parameter (k_{e0}) voor beide eindpunten het beste in staat de data te beschrijven. Dit suggereert dat de dynamiek vergelijkbaar is voor beide eindpunten.

Ondanks dat we niet aan hebben kunnen tonen dat het analgetische effect dat door ketamine wordt veroorzaakt onafhankelijk is van het dissociatieve effect, kunnen we niet met zekerheid uitsluiten dat tenminste een deel van het analgetische effect onafhankelijk is van de dissociatieve effecten. Daarnaast is het lastig de studies met elkaar te vergelijken, aangezien er verschillende pijntesten gebruikt zijn in onze studie (drukpijn test) en in de studie van Gitlin et al. (cuff pain test). Bij verschillende soorten pijn kunnen meerdere typen neuronale circuits betrokken zijn, waardoor de afhankelijkheid van de analgesie en dissociatieve effecten kan variëren tussen verscheidene soorten pijn. Een vergelijkbaar principe zou van toepassing kunnen zijn op de meting van de psychedelische/dissociatieve effecten, welke ook verschilden tussen beide studies.

TOEKOMST PERSPECTIEVEN

Aangezien er slechts een beperkt aantal adequate RCTs beschikbaar zijn welke de effectiviteit van i.v. ketamine bestuderen voor de behandeling van neuropathische pijn, zijn er nieuwe RCT data nodig zijn om definitieve conclusies te kunnen trekken. Hierbij was het opvallend dat geen van de tot op heden gepubliceerde RCTs onderscheid maken tussen verschillende type neuropathische pijn en verschillende onderzoekspopulaties. Aangezien bekend is dat overexpressie van een van de belangrijkste *target* receptoren, de NMDA receptor, betrokken is bij centrale sensitisatie, zouden toekomstige RCTs onderscheid kunnen maken tussen patiënten met en zonder centrale sensitisatie. Bovendien zou het, gezien de veelbelovende resultaten met experimentele (2*R*,6*R*)-

hydroxynorketamine behandelingen in muis modellen voor neuropathische pijn, interessant kunnen zijn om de behandeling met (2*R*,6*R*)-hydroxynorketamine nader te onderzoeken in een menselijke populatie. Echter wordt een dusdanige onderzoekopzet momenteel belemmerd doordat (2*R*,6*R*)-hydroxynorketamine tot op heden niet beschikbaar is voor gebruik in mensen.

In de meta-analyse konden we slechts een beperkt aantal potentiele covariaten testen. Onder andere doordat de data erg heterogeen waren, konden we effecten van auto-inhibitie na een bolus gift *versus* continue infusie, effecten van specifieke ziektebeelden of de rol van farmacogenetica op de farmacokinetiek van ketamine niet testen. Daarnaast zou het farmacokinetische model zoals het nu gepubliceerd is, kunnen worden onderworpen aan validatiestudies om de toepasbaarheid voor *target controlled infusion* systemen te testen.

Door het relatief korte tijdsframe waarin bloedmonsters zijn afgenomen en doordat het niet mogelijk was ketamine metabolieten direct toe te dienen, konden de metabole fracties (fracties van norketamine die naar respectievelijk dehydronorketamine of hydroxynorketamine omgezet worden) en centrale verdelingsvolumes van de metabolieten niet geschat worden. Daarnaast bevatte de data betrekkelijk weinig datapunten in de eliminatie fase van de secundaire metabolieten door het relatief korte tijdsframe waarin bloedmonsters zijn genomen. Bij het ontwerpen van toekomstige farmacokinetische studies, waarbij ook naar de secundaire metabolieten wordt gekeken, is het aan te raden gedurende een langere tijd te bemonsteren, bijvoorbeeld tot 24-48 uur na de laatste dosis. Bovendien zouden urine monsters genomen kunnen worden om een completer beeld te krijgen van de hoeveelheid ketamine die uiteindelijk wordt omgezet naar norketamine, hydroxynorketamine en dehydronorketamine.

In onze studie waarin werd gekeken naar de relatie tussen analgesie en de psychedelische effecten van ketamine, werd het analgetische effect gemeten aan de hand van een drukpijn test. Echter is dit soort (nociceptieve) pijn wellicht niet representatief voor de neuropathische pijn waar ketamine therapie mogelijk ook voor gebruikt zou kunnen worden. Om meer te weten te komen over de relatie tussen de dissociatieve effecten en analgesie in neuropathische pijn zouden toekomstige studies zich (deels) kunnen richten op neuropathische pijn patiënten.

CONCLUSIES

Gezien de getoonde data en analyses in dit proefschrift, kunnen de volgende conclusies worden getrokken:

1) Betrouwbare RCT's van goede kwaliteit die degelijk bewijs laten zien voor de *efficacy* van ketamine voor de behandeling van neuropathische pijn, zijn tot op heden zeer schaars.
2) De farmacokinetische *outputs* van het meta-analytische model en het ruwe data model zijn vergelijkbaar.
3) Na een initiële afname van ketamine plasma concentraties, zijn er nog significante metaboliet concentraties aanwezig, tot tenminste twee uur na het stoppen van de ketamine infusie.
4) Het is onwaarschijnlijk dat het verlichtende effect van natrium nitroprusside op de psychedelische bijwerkingen van ketamine veroorzaakt wordt door een farmacokinetisch mechanisme.
5) *S*-ketamine heeft een significant groter (positief) effect op de *cardiac* output dan *R*-ketamine.
6) Onze analyses hebben niet volledig uit kunnen sluiten dat in ieder geval een gedeelte van de analgetische effecten van ketamine onafhankelijk is van de psychedelische effecten.

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List of Publications
Curriculum Vitae

LIST OF PUBLICATIONS

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CURRICULUM VITAE

Jasper Kamp was born on the 3rd of October 1991 in Winschoten, the Netherlands. After completing secondary school (VWO, Dollard College, Winschoten) in 2009, he started his study Pharmacy at the *Rijksuniversiteit Groningen*. During his studies, he was involved in several research projects concerning drug metabolism and pharmacokinetic modelling. In addition, he combined his studies with a side-job at the UMCG hospital pharmacy for 5 years. In 2016, he started to combine his master *Pharmacy* with the research master *Medical Pharmaceutical Sciences* (specialization: "Toxicology and Drug Disposition").

During his life as a student, Jasper was actively involved in his student rowing club (A.G.S.R. Gyas) and was part of the Men's Heavyweight Rowing Crew in 2012.

Both master degrees were successfully completed in march 2018, after which he started his PhD in July 2018 at the Department of Anesthesiology at the LUMC under the supervision of prof. dr. A. Dahan and dr.ir. E. Olofsen. Since April 2018 the PhD was combined with a job as project pharmacist at the production facility of the LUMC hospital pharmacy. Currently, Jasper is working as a hospital pharmacist in training at the LUMC hospital pharmacy.