Ketamine pharmacometrics

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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.

REFERENCES

1. Niesters M, Dahan A: Pharmacokinetic and pharmacodynamic considerations for NMDA receptor antagonists in the treatment of chronic neuropathic pain. Expert Opin Drug Metab Toxicol 2012; 8: 1409-17
2. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, Benoliel R, Cohen M, Cruccu G, Davis KD, Evers S, First M, Giamberardino MA, Hansson P, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Nurmikko T, Perrot S, Raja SN, Rice ASC, Rowbotham MC, Schug S, Simpson DM, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ, Barke A, Rief W, Treede RD, Classification Committee of the Neuropathic Pain Special Interest G: The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 2019; 160: 53-59
3. Nielsen BN, Friis SM, Romsing J, Schmiegelow K, Anderson BJ, Ferreiros N, Labocha S, Henneberg SW: Intranasal sufentanil/ketamine analgesia in children. Paediatr Anaesth 2014; 24: 170-80
4. Kaufman MB: Pharmaceutical Approval Update. Pharm Ther 2019; 44: 251-254
5. Aiyer R, Mehta N, Gungor S, Gulati A: A Systematic Review of NMDA Receptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice. Clin J Pain 2018; 34: 450-467
6. Connolly SB, Prager JP, Harden RN: A systematic review of ketamine for complex regional pain syndrome. Pain Med 2015; 16: 943-69
7. Orhurhu V, Orhurhu MS, Bhatia A, Cohen SP: Ketamine Infusions for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Anesth Analg 2019; 129: 241-254
8. Michelet D, Brasher C, Horlin AL, Bellon M, Julien-Marsollier F, Vacher T, Pontone S, Dahmani S: Ketamine for chronic non-cancer pain: A meta-analysis and trial sequential analysis of randomized controlled trials. Eur J Pain 2018; 22: 632-646
9. Zhao J, Wang Y, Wang D: The Effect of Ketamine Infusion in the Treatment of Complex Regional Pain Syndrome: a Systemic Review and Meta-analysis. Curr Pain Headache Rep 2018; 22: 12
10. Bell RF, Eccleston C, Kalso EA: Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2017; 6: CD003351
11. Jonkman K, van de Donk T, Dahan A: Ketamine for cancer pain: what is the evidence? Curr Opin Support Palliat Care 2017; 11: 88-92
12. Kroin JS, Das V, Moric M, Buvanendran A: Efficacy of the ketamine metabolite (2R,6R)-hydroxynorketamine in mice models of pain. Reg Anesth Pain Med 2019; 44: 111-117
13. Dahan A, Olofsen E, Sigtermans M, Noppers I, Niesters M, Aarts L, Bauer M, Sarton E: Population pharmacokinetic-pharmacodynamic modeling of ketamine-induced pain relief of chronic pain. Eur J Pain 2011; 15: 258-67
14. Henthorn TK, Avram MJ, Dahan A, Gustafsson LL, Persson J, Krejcie TC, Olofsen E: Combined Recirculatory-compartmental Population Pharmacokinetic Modeling of Arterial and Venous Plasma S(+) and R(-) Ketamine Concentrations. Anesthesiology 2018; 129: 260-270

15. Ihmsen H, Geisslinger G, Schuttler J: Stereoselective pharmacokinetics of ketamine: R(-)-ketamine inhibits the elimination of S(+)-ketamine. Clin. Pharmacol. Ther. 2001; 70: 431-8

16. Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW: Enantioselective Pharmacokinetics of (R)- and (S)-Ketamine After a 5-Day Infusion in Patients with Complex Regional Pain Syndrome. Chirality 2011; 23: 138–143

17. Geisslinger G, Hering W, Kamp HD, Vollmers KO: Pharmacokinetics of ketamine enantiomers. Br J Anaesth 1995; 75: 506-507

18. Zhao X, Venkata SL, Moaddel R, Luckenbaugh DA, Brutsche NE, Ibrahim L, Zarate CA, Jr., Mager DE, Wainer IW: Simultaneous population pharmacokinetic modelling of ketamine and three major metabolites in patients with treatment-resistant bipolar depression. Br J Clin Pharmacol 2012; 74: 304-314

19. Jonkman K, van der Schrier R, van Velzen M, Aarts L, Olofsen E, Sarton E, Niesters M, Dahan A: Differential role of nitric oxide in the psychedelic symptoms induced by racemic ketamine and esketamine in human volunteers. Br J Anaesth 2018; 120: 1009-1018

20. Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, Brune K: Pharmacokinetics and Pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. Br J Anaesth 1993; 70: 666-671

21. Oye I: Effects of Ketamine on Sensory Perception: Evidence for a Role of N-Methyl-D-Aspartate Receptors. The journal of pharmacology and experimental therapeutics 1992; 260

22. Vollenweider FX, Leenders KL, Øye I, Hell D, Angst J: Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). European Neuropsychopharmacology 1997; 7: 25-38

23. Olofsen E, Sigtermans M, Noppers I, Niesters M, Mooren R, Bauer M, Aarts L, Sarton E, Dahan A: The dose-dependent effect of S(+)-ketamine on cardiac output in healthy volunteers and complex regional pain syndrome type 1 chronic pain patients. Anesth Analg 2012; 115: 536-546

24. Olofsen E, Noppers I, Niesters M, Kharasch E, Aarts L, Sarton E, Dahan A: Estimation of the contribution of norketamine to ketamine-induced acute pain relief and neurocognitive impairment in healthy volunteers. Anesthesiology 2012; 117: 353-64

25. Okamoto H, Hoka S, Kawasaki T, Okuyama T, Takahashi S: L-Arginine Attenuates Ketamine-induced Increase in Renal Sympathetic Nerve Activity. Anesthesiology 1994; 81: 137-146

26. Gitlin J, Chamadia S, Locascio JJ, Ethridge BR, Pedemonte JC, Hahm EY, Ibala R, Mekonnen J, Colon KM, Qu J, Akeju O: Dissociative and Analgesic Properties of Ketamine Are Independent. Anesthesiology 2020; 133: 1021-1028