Ketamine pharmacometrics

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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

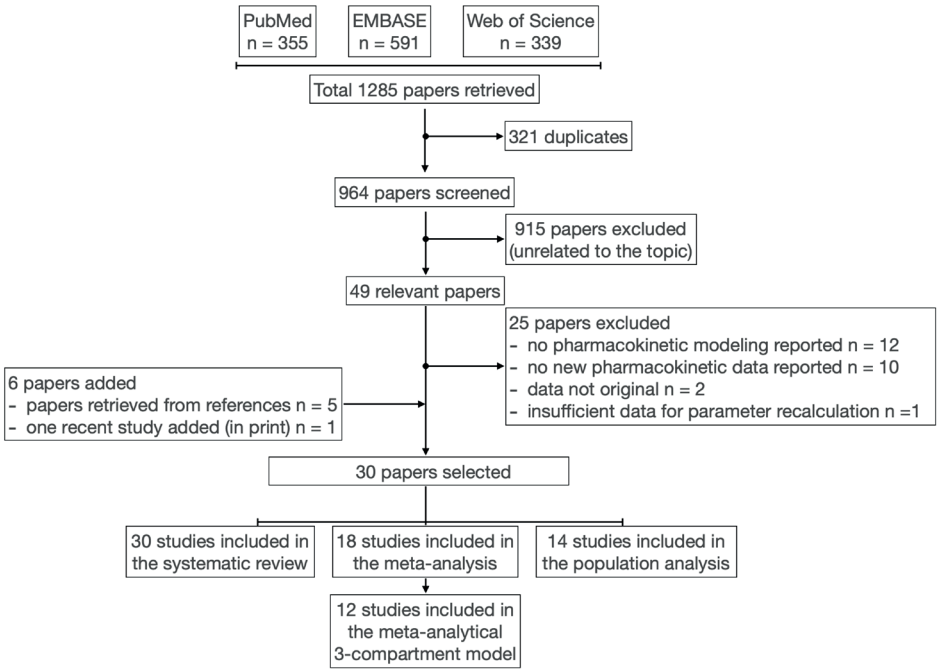

Figure 1. Schematic overview of the literature selection and performed analyses.

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).

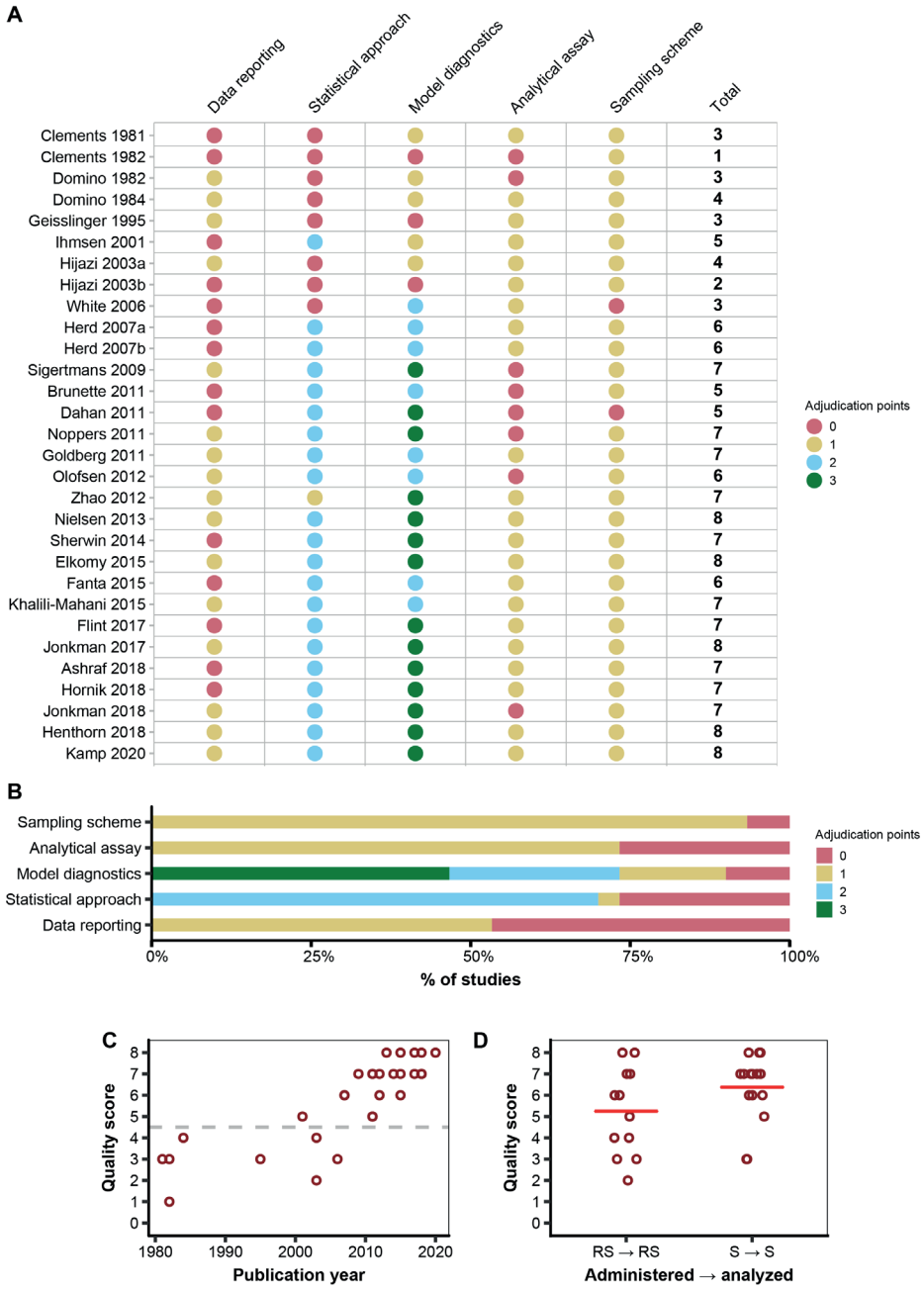

Figure 2. Adjudication of the extracted studies. Adjudication points given for data reporting, statistical approach, model diagnostics, analytical assay, sampling scheme for each of the included studies (**A**), overall distribution of study quality (**B**), study quality scores over the years (**C**) 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 %.

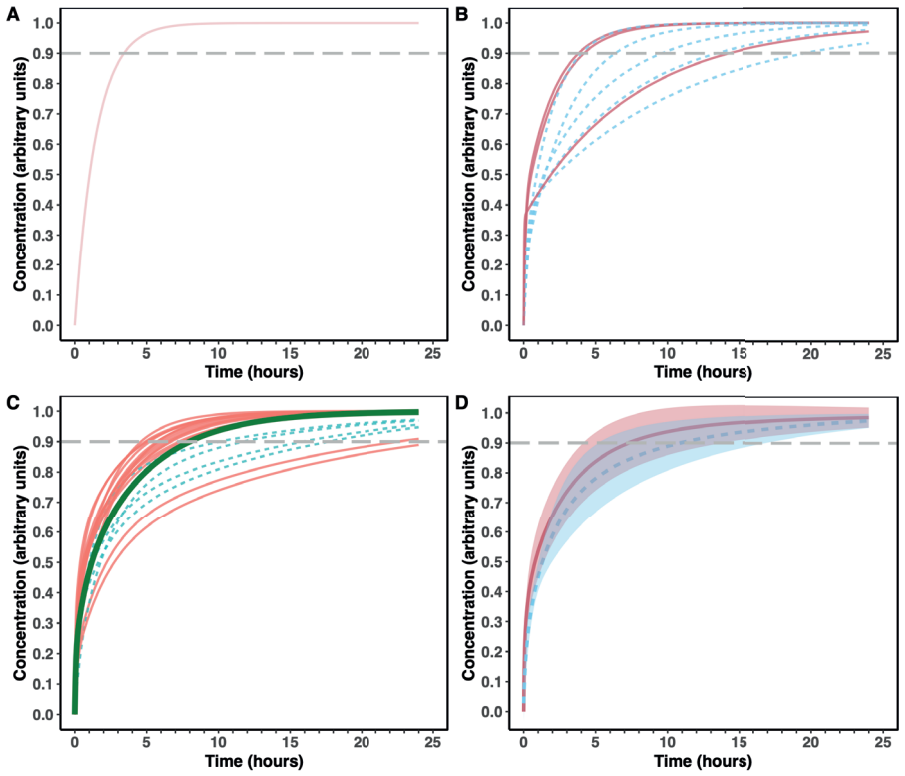

Figure 3. Simulations of the ketamine arterial (red) and venous (blue) plasma concentrations following the start of ketamine infusion towards a steady-state plasma concentration (arbitrarily set at 1.0). Data from one study using a one-compartment ketamine model (**A**), seven studies using a two-compartment 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]

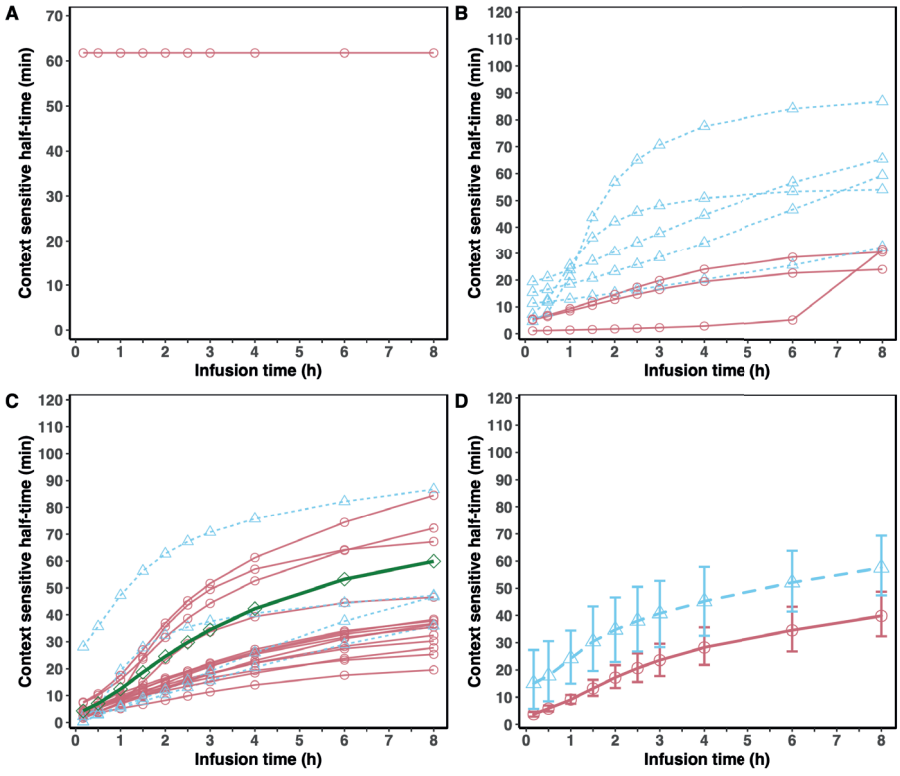

Figure 4. Ketamine context-sensitive half-time curves for each study. Red lines represent models based on arterial samples, blue lines models based on venous samples: (**A**) one-compartment models from one study, (**B**) two-compartment models from seven studies, and (**C**) three-compartment models 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

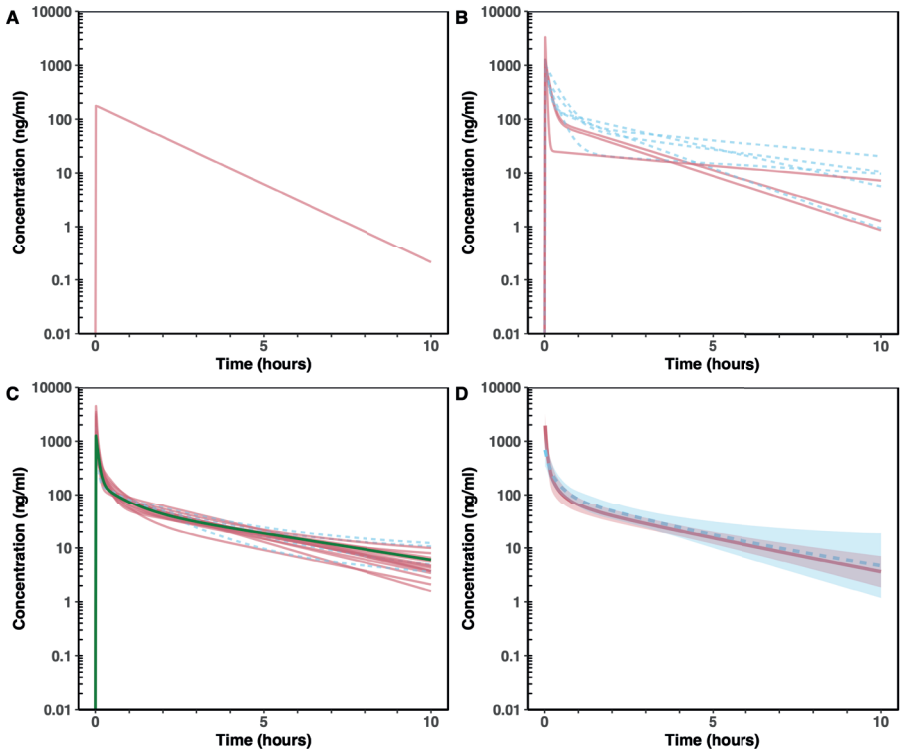

Figure 5. Ketamine wash-in/wash-out profiles of each study following a 1-min bolus infusion of 0.5 mg/kg in a 70 kg individual. Red lines represent models based on arterial samples, blue lines models based on venous samples: (**A**) one-compartment models from one study, (**B**) two-compartment models 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.

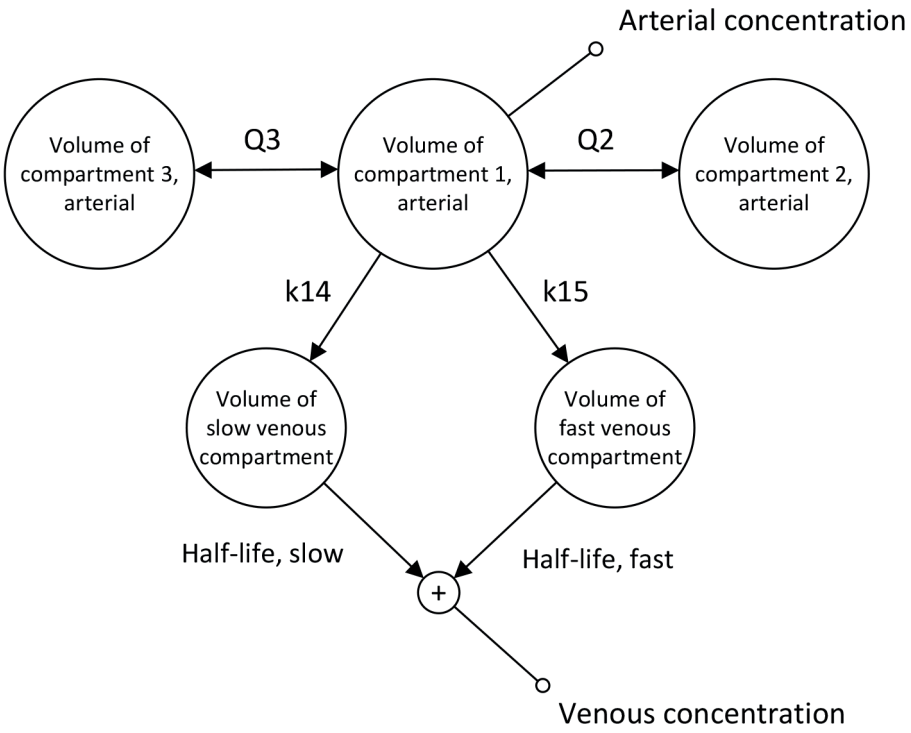

Figure 6. Schematic overview of the raw data model. The arterial concentrations ($C_{arterial}$) were modelled with a three compartmental model (with parameters V1-3$_{artarial}$) with intercompartmental clearances (parameters Q2 and Q3) and an elimination rate constant equal to the sum of parameters 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

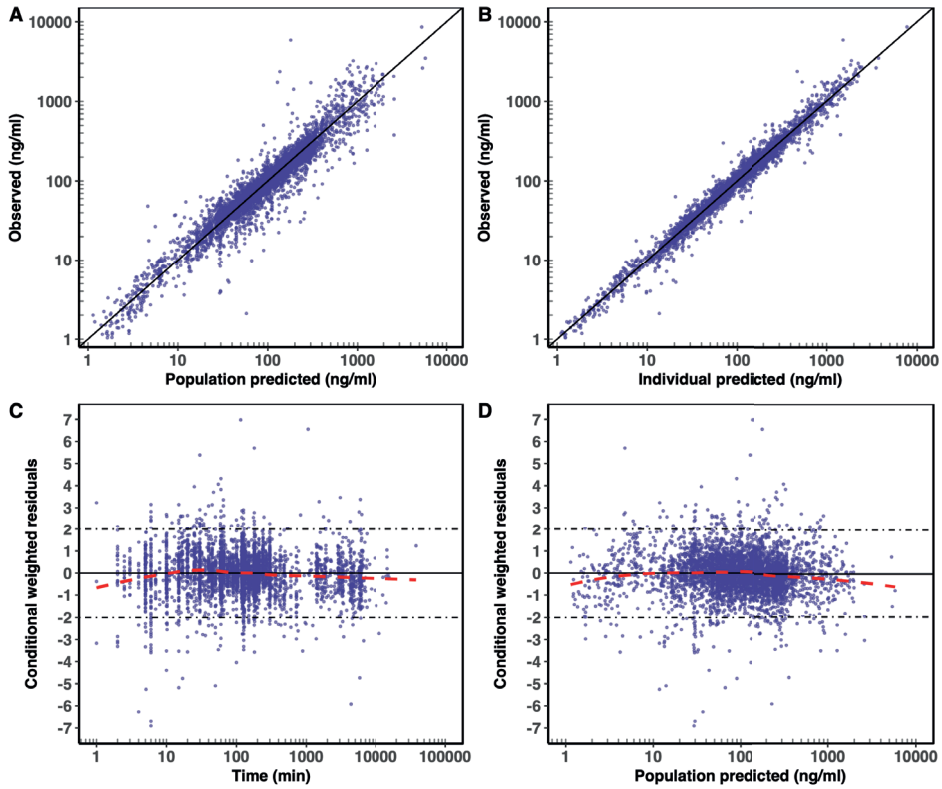

Figure 7. Goodness of fit plots of the raw data model. Observed *versus* population predicted (**A**), observed *versus* individual predicted (**B**), conditional weighted residuals *versus* time (**C**) and conditional weighted residuals *versus* population predicted (**D**).

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.

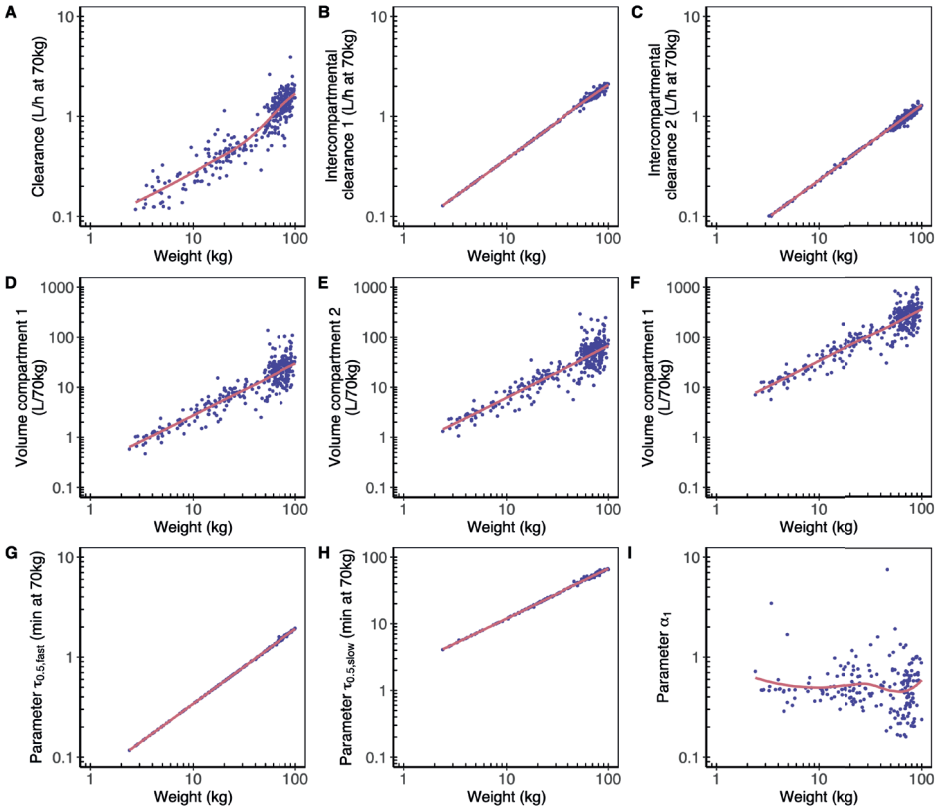

Figure 8. Parameter *versus* subject body weight plots. Clearance, and intercompartmental clearances 1 and 2 against subject body weight (**A-C**); Volume of compartment 1, compartment 2 and compartment 3 against subject body weight (**D-F**); fast and slow elimination half-lives against subject body 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.

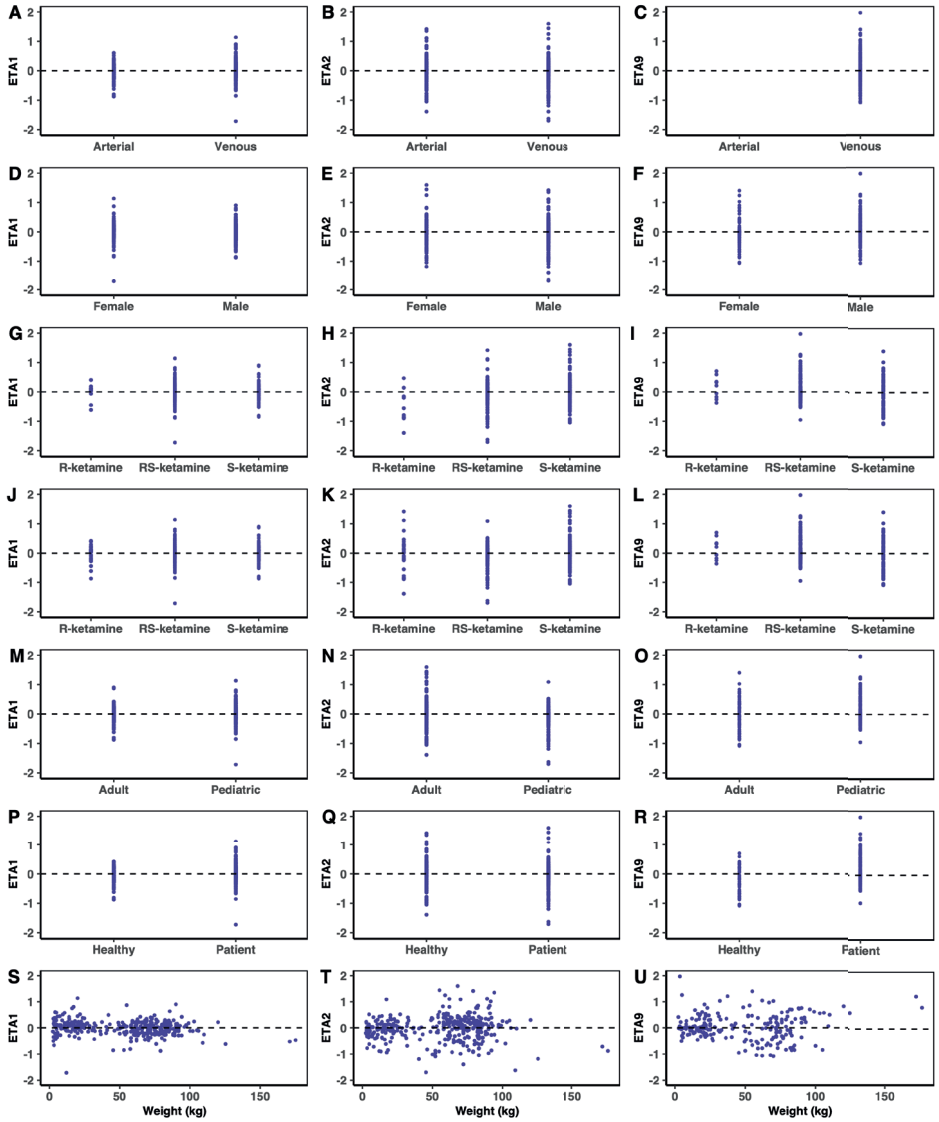

Figure 9. Post hoc ETAs *versus* covariates. Only non-fixed ETA values are shown. ETA1 = inter-individual variabilityfor clearance; ETA2 = inter-individual variability for volume of distribution; ETA9 = inter-individual variability for the $\alpha 1$ parameter. ETAs plotted against arterial versus venous 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**).

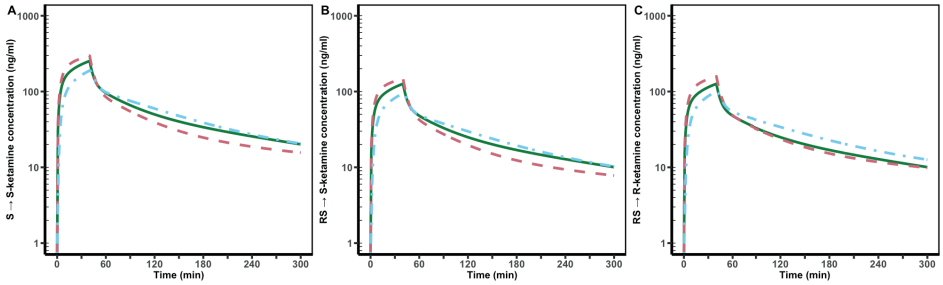

Figure 10. Simulated concentration time profiles with the three-compartment meta-analytical model (green line), and arterial (red line) and venous (blue line) population model derived from the raw data sets after a 40 min infusion of 0.5 mg/kg esketamine or racemic ketamine in a 70 kg person. Three scenarios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