Modeling the norketamine metabolite in children and the implications for analgesia

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Summary

Background: Norketamine, a metabolite of ketamine, is an analgesic with a potency one-third that of ketamine. The aim of this study was to describe norketamine pharmacokinetics in children in order to predict time–concentration profiles for this metabolite after racemic ketamine single dose and infusion administration. The possible analgesic potential resulting from norketamine concentration may then be predicted using simulation.

Methods: Ketamine and norketamine data were available from two sources: (i) children presenting for procedural sedation in an emergency department given ketamine 1–1.5 mg·kg⁻¹ IV as a bolus dose; and (ii) a literature search of those studies describing ketamine and norketamine time–concentration profiles after either IV or IM single-dose ketamine in adults and children. A population pharmacokinetic analysis was undertaken using nonlinear mixed effects models (NONMEM). A two-compartment (central, peripheral) linear disposition model was used to fit the parent drug. An additional metabolite compartment was linked to the central compartment by series of intermediate compartments to account for norketamine delayed formation. Norketamine volume of distribution was fixed equivalent to central volume. Simulation was used to predict norketamine time–concentration profiles in children given either ketamine as an i.v. bolus 2 mg·kg⁻¹ or as an analgesic infusion 0.2 mg·kg⁻¹·h⁻¹ for 24 h.

Results: The analysis comprised 621 observations from 70 subjects. There were 57 children (age 8.3, sd: 3.5 years, range: 1.5–14; weight 32.5, sd: 15.6 kg, range: 10.8–74.8) and 13 adults. Population parameter estimates for the parent drug, standardized to a 70 kg person using allometric models were central volume (V1) 22 (BSV 89.6%) l·70 kg⁻¹, peripheral volume of distribution (V2) 129 (30.9%) l·70 kg⁻¹, clearance other than that metabolized to norketamine (LOther) 47.8 (37.7%) l·h⁻¹·70 kg⁻¹, and intercompartment clearance (Q) 216 (54.5%) l·h⁻¹·70 kg⁻¹. The norketamine formation clearance (CL2M) was 12.4 (127%) l·h⁻¹·70 kg⁻¹, elimination clearance (CLM) was 13.5 (145%) l·h⁻¹·70 kg⁻¹, and the rate constant for intermediate compartments was 26.5 (59.1%) h⁻¹.

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Conclusions: Ketamine has a longer elimination half-life (2.1 h) than norketamine (1.13 h). Simulation suggested that norketamine contributes to analgesia for 4 h after 2 mg·kg\(^{-1}\) i.v. bolus, provided the assumption that a norketamine concentration above 0.1 mg·l\(^{-1}\) contributes analgesia is true. Similarly, the norketamine metabolite may contribute to analgesia for 1.5 h after low-dose infusion (0.2 mg·kg\(^{-1}\)·h\(^{-1}\)) cessation.

Keywords: norketamine; pharmacokinetics; children; allometrics; ketamine; analgesia

Introduction

The analgesic properties of ketamine are mediated by multiple mechanisms at central and peripheral sites. The contribution from N-methyl-D-aspartate (NMDA) receptor antagonism and interaction with cholinergic, adrenergic, serotonergic, opioid pathways, and local anesthetic effects remains to be fully elucidated. Data from rats suggest that the metabolite norketamine has potency one-third that of ketamine (1). The disposition of this metabolite in children is poorly described.

Ketamine is finding an increasing role as a coanalgesic infusion for intraoperative and postoperative pain control (2,3). The adult dose of 0.05–1 mg·kg\(^{-1}\)·h\(^{-1}\) has not been fully tested in children (4,5). Many clinicians are currently using 0.1–0.2 mg·kg\(^{-1}\)·h\(^{-1}\) alone or to supplement opioid therapy and this dose is not usually associated with hallucinations and dysphoria. The role of the norketamine metabolite in pain control after stopping ketamine infusion is not quantified.

This study aims to describe norketamine pharmacokinetics in order to predict serum concentrations in children given racemic ketamine infusion. The role this metabolite has in analgesia is elusive, but an understanding of time–concentration relationships may improve understanding of its analgesic potential.

Methods

Racemic etamine and the metabolite norketamine time–concentration profiles were available from seven discrete studies. The majority of patients were taken from a study investigating ketamine pharmacokinetics in children undergoing procedural sedation in an emergency department (6). However, study duration was approximately 30 min and was inadequate for investigation of norketamine clearance unless supported by data from other sources. These pediatric data were supplemented by additional richer data gleaned from the literature.

Study 1

Residual samples from a study investigating ketamine pharmacokinetics in children undergoing procedural sedation in an emergency department were assayed for norketamine concentration. Children were given 1–1.5 mg·kg\(^{-1}\) i.v. ketamine. There were 54 children (age 8.3, SD: 3.5 years, weight 32.5, SD: 15.6 kg) available for study (6). Samples were taken 2–5 min after ketamine administration, at midpoint during the procedure and a last sample as late as possible after the procedure. If the sedating physician felt the child needed a further dose of ketamine before beginning the surgical procedure then an additional sample was collected 2–5 min after this dose.

Assays were performed using solid phase extraction (SPE). An aqueous solution (50 μl) of the internal standards ketamine-d\(_4\)·HCl (2 μg·ml\(^{-1}\)) and norketamine-d\(_4\)·HCl (0.6 μg·ml\(^{-1}\)) was added to each aliquot of blood specimen (0.2 ml). 3 ml phosphate buffer (0.1 mM, pH 6) was added and the resulting solution was sonicated for 15 min, centrifuged and applied to a pretreated Strata\textsuperscript{TM}X polymeric SPE column (200 mg, 3 ml (Phenomenex, Torrence, CA, USA)).
The column was sequentially rinsed with 2 ml portions of water, acetic acid (0.01 M) and 5% aqueous acetonitrile. After drying the column the analytes were eluted with 2 ml of 0.01 M acetic acid in acetonitrile. The eluate was evaporated to dryness under nitrogen and the residue reconstituted in 4 ml acetonitrile/0.01 M ammonium formate (1:1).

Analyses were conducted using a Shimadzu 10AVP HPLC system (Shimadzu Corporation, Kyoto, Japan) attached to a PE Sciex API 300 triple quadrupole mass spectrometer equipped with a Turbolon spray source. The HPLC column was a Phenomenex Luna 3μ Phenyl-hexyl column, 2×50 mm, with a 4×2 mm Phenomenex Phenyl-propyl guard column. The mobile phase was a gradient of acetonitrile and 10 mM ammonium formate. The injection volume was 10 μl.

The mass spectrometer was used in the positive ion MRM mode. Transition ions were 238 of 220 for ketamine (242 of 211 for d4), 224 of 207 for norketamine (228 of 211 for d4). Confirmatory transitions of 238 of 207 and 224 of 179 were monitored for ketamine and norketamine, respectively.

Six-point standard curves were constructed over the concentration ranging from 0.125 to 4.5 μg·ml⁻¹ for ketamine and 0.06 to 2.0 μg·ml⁻¹ for norketamine, by spiking drug-free blood with aqueous solutions of the analytes.

The intraday reproducibility for ketamine (six replicates) at 0.25 μg·ml⁻¹ had a coefficient of variation (CV) of 5%. The interday CV (3 days) was 4%. For norketamine the corresponding figures at 0.12 μg·ml⁻¹ were 10% and 8%.

Study 2

Wieber et al. (7) studied five adult patients who were given ketamine 2.5 mg·kg⁻¹. These patients had no liver damage or renal insufficiency. Venous blood was sampled at 10, 30, 60, 90, 120, 180, 240, 360, 540, and 720 min after administration. The analysis of ketamine and its metabolites was performed using gas–liquid chromatography for separation and flame ionization detection. The lower limit of quantification for ketamine in serum was 0.025 mg·l⁻¹. Pooled data were extracted from Figure 3 of this paper. Information contributed one naïve pooled ‘subject’.

Study 3

Ketamine and norketamine time–concentration profiles for seven adult patients (ASA I–III, age 45, sd: 9.3 years; weight 64.3, sd: 10.1 kg) undergoing anesthesia who were given 2–2.2 mg·kg⁻¹ ketamine i.v. are reported in Table 3 of Domino et al.’s paper (8). Blood samples were withdrawn from a separate venous line at 1, 2, 5, 10, 15, 20, and 30 min, and 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 h. A sensitive gas chromatographic–mass fragmentographic assay for ketamine and its metabolites was used (9). Unlike other studies, these seven patients suffered significant pathology that included Crohn’s disease, carcinoma, lower urinary tract obstruction and nasal polyps.

Study 4

Healthy male prisoners (mean age 32.3 years, range: 26–41; mean weight 72.8, range: 59.9–81.1 kg) were given ketamine IV 2.2 mg·kg⁻¹ with and without diazepam using a double-blind, randomized, crossover design (10). Samples for assay were collected at 1, 2, 3, 4, 5, 10, 20, and 30 min and 1, 2, 4, 5, 6, 8, 12, and 24 h. Pooled mean data for ketamine and norketamine are presented in Tables I and II of that paper and this information contributed two naïve pooled ‘subjects’. Gas chromatography–mass fragmentography was used to assay blood samples for ketamine and norketamine (9).

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<th>Parameter</th>
<th>Estimate</th>
<th>%BSV</th>
<th>%SE</th>
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BSV, the between-subject parameter variability; %SE, the standard error of the estimate.
Study 5

Grant et al. (11) investigated six fasting healthy adult volunteers (age 31.8, SEM: 2 years, weight 70.7, SEM: 4.4 kg) who were administered sequentially oral ketamine (0.5 mg·kg\(^{-1}\)) and IM ketamine (0.5 mg·kg\(^{-1}\)) and placebo 1 week apart. Venous blood was taken for ketamine and norketamine assay at 15-min intervals for 2 h. Pooled data after IM ketamine are illustrated in Figure 2 of that paper. Gas–liquid chromatography with electron capture detection was used to measure ketamine and metabolite concentrations (12). These pooled data from adults given IM ketamine contributed one naïve pooled ‘subject’.

Study 6

Grant et al. (13) describe pooled data from five adults (ages 37–76 years, mean 52 years; weight 55–88 kg, mean 69 kg) and four children (ages 5–9 years, mean 6.1 years; weight 19–24 kg, mean 21.5 kg) given ketamine 2 mg·kg\(^{-1}\) i.v. An additional three adults (ages 24, 29, and 69 years; weights 74, 55, and 62 kg) and five children (ages 4–9 years, mean 6.9 years; weight 13–23 kg, mean 18.9 kg) were given 6 mg·kg\(^{-1}\) IM. These subjects underwent minor elective orthopedic or general surgery and anesthesia was maintained with halothane. Pooled data for ketamine and norketamine, sampled at 5, 15, 30, 60, 180, and 300 min are presented in Tables I and III of that paper. Plasma was separated and stored at ~20°C until assay by gas–liquid chromatography (12). These pooled data contributed two adult and two child naïve pooled ‘subjects’.

Study 7

Pooled data from eight children (mean age 4.8, range: 3–9 years; mean weight 18.4, SD 4.7 kg) given ketamine i.v. 3 mg·kg\(^{-1}\) are illustrated in Figure 1 of a paper describing ketamine pharmacokinetics in children (14). Ketamine was administered 15 min before the end of an anesthetic maintained with halothane. Venous samples for ketamine and

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**Table 2**

<table>
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<td>(V_m = V_1)</td>
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BSV, the between-subject parameter variability; SE, the standard error of the estimate.

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**Figure 1**

The pharmacokinetic model. A two-compartment (central, peripheral) linear disposition model was used to fit the parent drug. An additional compartment for metabolite was linked to the central compartment by series of intermediate compartments to account for norketamine formation time delays. Norketamine volume of distribution was fixed equivalent to central volume. CL\(_2\)M is formation clearance of norketamine metabolite CLother is clearance of ketamine by other routes (total ketamine elimination clearance = CL\(_2\)M + CLother), Q is intercompartment clearance, V1 is central volume of distribution, V2 is peripheral volume of distribution, CLM is elimination clearance of norketamine metabolite, Rate Mx is the rate constant for intermediate compartments, and ka is the absorption rate constant after intramuscular administration.
metabolite assay were taken at 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, and 360 min. These data contributed one pediatric naïve pooled ‘subject’. Ketamine and norketamine were measured by gas–liquid chromatography. Calibration curves were linear within the range of 0–2 mg l⁻¹. The standard variations for ketamine and norketamine were, respectively, 4.4% and 6.9% for 0.02 mg l⁻¹, and 1.7% and 3.4% for 2 mg l⁻¹.

Pharmacokinetic analysis

Population parameter estimations

A two-compartment (central, peripheral) linear disposition model was used to fit the parent drug. An additional metabolite compartment was linked to the central compartment by a series of intermediate compartments to account for norketamine formation time delays. Norketamine volume of distribution ($V_m$) was fixed equivalent to central volume (Figure 1).

Population parameter estimates were obtained using nonlinear mixed effects modeling (NONMEM; 15). This model accounts for population parameter variability (between- and within-subjects) and residual variability (random effects) as well as parameter differences predicted by covariates (fixed effects). The population parameter variability in model parameters was modeled by a proportional variance model. An additive and a proportional term were used to characterize the residual unknown variability. A separate set of residual errors was used to distinguish our own study from those taken from literature. The population mean parameters, between subject variance, and residual variance were estimated using the first-order conditional interaction estimate method differential equations using ADVAN6 TOL5 of NONMEM V. Convergence criterion was three significant digits. A COMPAQ DIGITAL FORTRAN Version 6.6A compiler with Intel Celeron 333 MHz CPU (Intel Corp., Santa Clara, CA, USA) under MS Windows XP (Microsoft Corp., Seattle, WA, USA) was used to compile NONMEM.

The population parameter variability is modeled in terms of random effect ($\eta$) variables. Each of these variables is assumed to have mean 0 and a variance denoted by $\omega^2$, which is estimated.

The covariance between two elements of $\eta$ (e.g. $\eta_{CL}$ and $\eta_V$) is a measure of statistical association between these two variables. Their covariance is related to their correlation ($R$), i.e.

$$ R = \frac{\text{covariance}}{\sqrt{\omega_{CL}^2 \times \omega_V^2}} $$

The covariance of parameter variability was incorporated into the model.

Covariate analysis

The parameter values were standardised for a body weight of 70 kg using an allometric model (16,17).

$$ P_i = P_{std} \times \left( \frac{W_i}{W_{std}} \right)^p $$

where $P_i$ is the parameter in the $i$th individual, $W_i$ is the weight in the $i$th individual and $P_{std}$ is the parameter in an individual with a weight $W_{std}$ of 70 kg. This standardization allows comparison of child parameter estimates with those reported for adults. The $P$ exponent was 0.75 for clearance, 0.25 for half times and 1 for distribution volumes (18–21).

The quality of fit of the pharmacokinetic model to the data were sought by NONMEM’s objective function and by visual examination of plots of observed vs predicted concentrations. Models were nested and an improvement in the objective function was referred to the chi-squared distribution to assess significance, e.g. an objective function change (OBJ) of 3.84 is significant at $\alpha = 0.05$.

Simulation

A simulation study was performed to investigate ketamine and norketamine concentration variability in children given a single dose of i.v. ketamine 2 mg kg⁻¹ i.v. and infusion 0.2 mg kg⁻¹ for 24 h. Simulated children ($n = 1000$) were aged 8.3, ±3.5 years (range: 1.5–14) and weight 32.5, ±15.6 kg (range: 10.8–74.8). Pharmacokinetic parameter estimates and their variability from this current analysis were used to predict individual time–concentration profiles.

Results

The analysis comprised 621 observations from 70 subjects. There were 57 children (age 8.3, ±3.5 years, range: 1.5–14; weight 32.5, ±15.6 kg, range: 10.8–74.8) and 13 adult subjects. Population parameter estimates for the parent drug, standardized to a 70 kg person using allometric models were
central volume (V1) 22 (BSV 89.6%) 1.70 kg\(^{-1}\), peripheral volume of distribution (V2) 129 (30.9%) 1.70 kg\(^{-1}\), clearance other than that metabolised to norketamine (CL\(_{\text{other}}\)) 47.8 (37.7%) l\(\text{h}\)\(^{-1}\) 70 kg\(^{-1}\) and intercompartment clearance (Q) 216 (54.5%) l\(\text{h}\)\(^{-1}\) 70 kg\(^{-1}\). These estimates are shown in Table 1. The norketamine formation clearance (CL\(_{2M}\)) was 12.4 (127%) l\(\text{h}\)\(^{-1}\) 70 kg\(^{-1}\), elimination clearance (CL\(_{M}\)) was 13.5 (145%) l\(\text{h}\)\(^{-1}\) 70 kg\(^{-1}\) and the rate constant for intermediate compartments 26.5 (59.1%) h\(^{-1}\) (Table 2). The correlation of between parameter variability (Table 3), introduced to increase stability of the model, was low for all except for those relating CL\(_{2M}\) and CL\(_{M}\) and V1. Residual errors for both the analysis of data from our own study and from literature data analysis were similar for ketamine. The proportional error for literature norketamine estimates was three times that of our own data.

Figure 2a,b demonstrate the quality of fit of pharmacokinetic data for the parent drug, ketamine. Figure 2a shows three rather high observed ketamine concentrations where there is marked discrepancy from the population prediction. Individual Bayesian predictions (Figure 2b) were satisfactory. These three observations were all sampled at 1 min; two were from pooled data in adult prisoners (10), and the third from an adult undergoing prostate surgery (8). Figure 3a,b demonstrate the quality of fit of pharmacokinetic data for the metabolite, norketamine. Individual concentration predictions are based on values of maximum a posteriori Bayesian estimates of the parameters using the posthoc option while predicted typical (population) concentrations are based on population parameters and covariate information. Predictions from NONMEM’s posthoc (posterior individual) step are based on values of the parameters for the specific individual using their observed data.

There were no changes in ketamine clearance or volume of distribution with age. Adult ketamine and norketamine estimates were indistinguishable from pediatric estimates after standardization for size (Figure 4a,b). Patients from study 3 displayed greatest clearance variability. One 42-year-old, 54.5 kg male with Crohn’s disease had a clearance twice that of the population mean, while another 57-year-old, 55.9 kg female with endometrial carcinoma had low clearance.

Ketamine and norketamine median-concentration profiles and 95% CIs for 1000 simulated children (age range: 1.5–14 years, weight range: 10.8–74.8 kg) given an i.v. ketamine 2 mg\(\text{kg}\)\(^{-1}\) bolus are illustrated in Figure 5a,b is drawn using the assumption that norketamine has a potency 1/3 that of ketamine and so the abscissa represents this combined ‘effective’ concentration. This combined ‘effective’

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**Table 3**
The correlation of parameter between-subject variability

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<th></th>
<th>CL</th>
<th>V1</th>
<th>V2</th>
<th>Q</th>
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<th>CL(_{M})</th>
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CL, total ketamine elimination clearance; Q, intercompartment clearance; V1, central volume of distribution; V2, peripheral volume of distribution; CL\(_{2M}\), formation clearance of norketamine metabolite; CL\(_{M}\), elimination clearance of norketamine metabolite; Rate MI, the rate constant for intermediate compartments.
concentration is above 0.1 mg\textsuperscript{l} for 4 h after bolus administration. Figure 6a shows ketamine and norketamine median-concentration profiles and 95\% CIs with infusion of 0.2 mg\textsuperscript{kg\textsuperscript{h}}\textsuperscript{1} over 24 h. The median steady-state concentration is 0.15 mg\textsuperscript{l}. A median-concentration above 0.1 mg\textsuperscript{l} is maintained for 30 min after stopping infusion. Figure 6b demonstrates the combined ‘effective’ concentration. The median combined ‘effective’ steady-state concentration is 0.19 mg\textsuperscript{l} and concentrations are above 0.1 mg\textsuperscript{l} for 1.5 h after stopping infusion.

**Discussion**

We present pharmacokinetic parameter estimations that predict norketamine concentrations after racemic ketamine administration. Norketamine pharmacokinetics are rarely described. Wieber *et al.* (7) report an elimination half-life of 3.99 (SD 1.23) h in adults during anesthesia and Hijazi *et al.* (22) report
an elimination half-life of 5.3 (± 1.7) h in intensive care patients, but this information contributes little to an understanding of metabolite formation or steady-state concentration after ketamine dosing in children. The reported norketamine elimination half-life is longer than that reported for ketamine (approximately 2.5 h; 7, 8, 10–14, 23), suggesting a decreased elimination of norketamine relative to the parent drug. Our analysis does not support this suggestion. Ketamine (\(T_{1/2}\) elimination 2.1 h) has a longer elimination half-life than norketamine (\(T_{1/2}\) elimination 1.13 h).

Ketamine low-dose infusion (0.1–0.2 mg·kg\(^{-1}\)·h\(^{-1}\)) is used for postoperative pain control in children to complement morphine analgesia and decrease unwanted side effects (2, 3, 24). We used simulation to assess the impact the norketamine metabolite might have on analgesia after low-dose infusion using the assumptions that norketamine has analgesic effectiveness 1/3 that of its parent (1) and that pain thresholds are elevated at 0.1 mg·l\(^{-1}\) (12). It is possible that this metabolite may contribute analgesia for an additional hour only after stopping infusion, although effect site concentration–analgesic relationships for ketamine and norketamine have not been described.

Both raw data and naïve pooled data were used in the analyses. Pooled data are used in classical PK studies and compare well with estimates from population methods when rich data are used (25). Ketamine parameter estimates are similar to those reported previously in children (13, 14). The concurrent ketamine/norketamine analysis and the addition of richer data from the literature to our own relatively sparse truncated data generated a lower clearance (CL\(_{\text{total}}\) 60.2 h\(^{-1}\)·70 kg\(^{-1}\)) than we previously reported (90 h\(^{-1}\)·70 kg\(^{-1}\); 6). Parameter estimates from that earlier analysis accurately described disposition over the short (approximately 30 min) time course studied, but assay sampling study design was compromised by the restricted study time available in children undergoing outpatient procedures. The children studied were healthy individuals undergoing minor surgical procedures. Adult subjects comprised both healthy and diseased and also displayed greater parameter variability. One 42-year-old male with Crohn’s disease, a systemic disorder associated with increased metabolic rate, had a clearance twice that of the population mean, while another 57-year-old female with endometrial carcinoma had a low clearance. The extent of this carcinoma or its impact on hepatic function was not reported. Nor is any information available about concomitant drug therapy in these adults. There were three high observed ketamine concentrations where there was marked discrepancy from the population prediction (Figure 2a). Possible causes for this discrepancy include an error of accuracy of the 1-min sampling time or model misspecification. A three-compartment model could fit these earlier predictions better. However, the existence of limited early data failed to justify the selection of a three-compartment model and the risk of overparameterization supported rejection of a three-compartment model. Good predictive ability for the metabolite (our primary objective)
was achieved with the two-compartment model used.

We were unable to show metabolite formation or elimination clearance changes with age in this current study involving children out of infancy (>1 year). Pediatric estimates were similar to adult estimates after standardization for size using allometric scaling. The clearance formation (CL2M) enzyme responsible for ketamine N-demethylation to norketamine is CYP3A4 (26). Maturation of this enzyme occurs within the first year of life (27). Pharmacogenetic influences and concomitant drug therapy (e.g. induction of CYP3A4 with alcohol, inhibition with fluconazole, omeprazole, cimetidine) affect clearance. We might expect maturation of the metabolite clearance pathway (CLM) to mirror renal maturation, which occurs also over the first year of life (28, 29). Precision, bias, and minimal quantifiable concentration for literature assay techniques were rarely reported. The residual proportional error for these data was three times that of our own data, reflecting greater uncertainty in literature estimates.

Norketamine is not detectable in serum for approximately 2–5 min after ketamine administration i.v. (7,8,10,23). Our PK model incorporated a chain of intermediate metabolite elimination compartments to account for delayed formation clearance (Figure 1). The norketamine volume of distribution (V_m) and the proportion of ketamine cleared by formation to norketamine are unknown; this V_m was fixed equal to V1 for this current study. Wieber et al. (7) report that the urinary cumulative excretion of norketamine within 24 h was only 1.62 (SD 0.19) % of administered dose. The other major metabolite, dihydronorketamine achieved a cumulative excretion of 16.1 (SD 2.25) % of the dose after 72 h (7). The remaining drug is excreted unchanged in urine or feces, excreted as a conjugate of glucuronic acid (7), or sequestered in body tissues (10). The amount of ketamine metabolized to norketamine remains vague.

Ketamine has a longer elimination half-life (2.1 h) than norketamine (1.13 h) and our current pharmacokinetic findings suggest that norketamine will not have prolonged or major effect after either single i.v. bolus or infusion dosing. The pharmacodynamics of norketamine in adults and children are indeterminate and currently predicted from rodent studies.

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References


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