Pharmacokinetics and Bioavailability of Inhaled Esketamine in Healthy Volunteers

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ABSTRACT

Background: Esketamine is traditionally administered *via* intravenous or intramuscular routes. In this study we developed a pharmacokinetic model of inhalation of nebulized esketamine with special emphasis on pulmonary absorption and bioavailability.

Methods: Three increasing doses of inhaled esketamine (dose escalation from 25 to 100 mg) were applied followed by a single intravenous dose (20 mg) in 19 healthy volunteers using a nebulizer system and arterial concentrations of esketamine and esnorketamine were obtained. A multicompartmental pharmacokinetic model was developed using population nonlinear mixed-effects analyses.

Results: The pharmacokinetic model consisted of three esketamine, two esnorketamine disposition and three metabolism compartments. The inhalation data were best described by adding two absorption pathways, an immediate and a slower pathway, with rate constant $0.05 \pm 0.01 \ \text{min}^{-1}$ (median ± SE of the estimate). The amount of esketamine inhaled was reduced due to dose-independent and dose-dependent reduced bioavailability. The former was 70% ± 5%, and the latter was described by a sigmoid E_{MAX} model characterized by the plasma concentration at which absorption was impaired by 50% (406 ± 46 ng/ml). Over the concentration range tested, up to 50% of inhaled esketamine is lost due to the reduced dose-independent and dose-dependent bioavailability.

Conclusions: We successfully modeled the inhalation of nebulized esketamine in healthy volunteers. Nebulized esketamine is inhaled with a substantial reduction in bioavailability. Although the reduction in dose-independent bioavailability is best explained by retention of drug and particle exhalation, the reduction in dose-dependent bioavailability is probably due to sedation-related loss of drug into the air. **(ANESTHESIOLOGY 2017; 127:675-83)**

THE *N*-methyl-D-aspartate receptor antagonist ketamine is a potent analgesic and antidepressant, increasingly used at subanesthetic doses to treat different forms of pain, as well as depression.[1–3] Currently the intravenous route is the predominant form of ketamine delivery with inherent need for a successful, sterile venipuncture by skilled healthcare personnel. This may prevent the use of ketamine for chronic therapy in several settings, such as palliative and geriatric care, as well as for acute therapy in preclinical emergency medicine and at remote locations. Inhalational ketamine delivery would circumvent the limitations associated with intravenous delivery because it allows a quick, easy, and painless treatment approach in nonclinical settings. In addition, aerosolized ketamine inhalation potentially results in rapid absorption into the systemic circulation with the fastest uptake of any route of delivery other than intravenous.[4] Although several studies have shown the feasibility and bioavailability of aerosolized opioid inhalation, published

human data on nebulized ketamine inhalation are sparse and preliminary. In these studies, nebulized ketamine was successfully administered to postoperative adult patients

What We Already Know about This Topic

- Ketamine is usually administered intravenously or intramuscularly
- Inhalation of preservative-free esketamine through a nebulizer system by spontaneously breathing subjects delivered a potentially active dose rapidly, with few serious adverse effects

What This Article Tells Us That Is New

- A simple compartmental pharmacokinetic model characterized the disposition of both inhaled and intravenous esketamine in volunteers
- There were two distinct pulmonary absorption pathways, a rapid one and one from which ketamine was released slowly
- Inhaled ketamine bioavailability was reduced due to both dose-independent and dose-dependent impairment of pulmonary uptake

to relieve sore throat and in preoperative pediatric patients to induce sedation.[5–7]

We performed a study on esketamine inhalation in healthy volunteers. We previously published part of the data focusing on safety and feasibility[8]; here we report the modeling analysis of the data. We administered three increasing doses of inhaled esketamine followed by a single intravenous dose in healthy volunteers and obtained arterial concentrations of ketamine and its main metabolite norketamine. The study had two parts: in part one the concentration of the inhalant remained constant (5 mg/ml) and the volume of the inhalant was increased in subsequent inhalation episodes (from 5 to 10 ml); in part two the inhaled volume remained constant (5 ml) and the esketamine concentration increased in the subsequent inhalation episodes (from 5 to 20 mg/ml). The main aim of the study was to develop a population pharmacokinetic model to characterize the bioavailability, pulmonary absorption, and disposition of inhaled esketamine. A descriptive analysis of part one of the study was published earlier.[8] In that article the feasibility and safety of esketamine inhalation were studied.

Materials and Methods

Ethics

After the local human ethics committee (Leiden University Medical Center, Leiden, The Netherlands) and the Central Committee on Research Involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, The Hague, The Netherlands) had approved the protocol, participants were recruited by flyers posted on the Leiden University campus (Leiden, The Netherlands). Before enrollment, written informed consent was obtained from all of the subjects. The study was registered in the Dutch trial register (No. 5358).

Participants

Subjects of either sex aged 18 to 39 yr and with a body mass index less than 30 kg/m^2 were eligible to participate in the study. An independent physician screened all of the subjects before enrollment. Exclusion criteria included a positive drug screen on the day of screening or on the day of testing; presence or history of any medical, neurologic, or psychiatric disease; pregnancy/lactation in women; a history of illicit drug use or weekly alcohol intake more than 21 units per week; participation in another trial in the three months before enrollment; current use of any medication; and abnormalities observed during physical examination. The subjects were asked to refrain from food and drinks for at least 8 h before the inhalation of ketamine started. In addition, participants were not allowed to consume caffeinated drinks such as coffee, black tea, or cola drinks; energy drinks; or chocolate for the 24 h before the study. Finally, all of the subjects were requested to refrain from tonic and grapefruit-containing food or beverages during the 7 days preceding the study day.

On the study day, an intravenous catheter was placed for drug administration and an arterial line in the left or right radial artery for blood sampling. During the study the subjects were continuously monitored (three-lead electrocardiogram and oxygen saturation).

Study Design

This open-label phase one study had two parts. In both parts subjects inhaled three increasing doses of nebulized preservative-free esketamine (Ketanest-S 5 mg/ml, Eurocept BV, Ankeveen, The Netherlands; Ketanest-S 25 mg/ml, Pfizer Pharma, Berlin, Germany), followed by an intravenous esketamine administration, with at least 60 min in between inhalations and between the last inhalation and intravenous infusion. In part one the subjects inhaled 25.0 mg (volume, 5 ml; concentration, 5 mg/ml; target inhalation duration = 10 min), followed by 37.5 mg (7.5 ml; 5.0 mg/ml; target inhalation duration = 15 min) and 50.0 mg (10 ml; 5 mg/ml; target inhalation duration = 20 min) nebulized esketamine and subsequently received 20.0 mg esketamine intravenously (16 ml; 1.25 mg/ml; infusion = 20 min). In part two, another set of subjects inhaled 25 mg (5 ml; 5 mg/ml; target inhalation duration = 15 min), 50 mg (5 ml; 10 mg/ml; target inhalation duration = 15 min), and 100 mg (5 ml; 20 mg/ml; target inhalation duration = 15 min) nebulized esketamine and subsequently received 20 mg esketamine intravenously (16 ml; 1.25 mg/ml; infusion 20 min).

To inhale the drug, we used a commercial nebulizer system (Aerogen Ultra, Medicare Uitgeest BV, Uitgeest, The Netherlands), which uses a palladium high-frequency vibrating mesh (Aerogen Solo Nebulizer, Medicare Uitgeest BV) to aerosolize (with particle size between 0.4 and 4.4 µm) the liquid ketamine and deliver a predefined quantity of drug to the spontaneously breathing subject. We attached the outlet of the device to the main venting system of the laboratory. Because the system uses a mouthpiece to deliver the aerosol, we placed a clip on the nose during inhalations to prevent nose breathing.

Blood Sampling and Measurement of Esketamine and Esnorketamine Concentrations

To quantify the esketamine and esnorketamine plasma concentrations, arterial blood samples were collected in 6-ml heparin tubes. The target and actual blood sampling times are given in table 1. Plasma samples were analyzed using validated high-performance liquid chromatography. The exact procedure has been described previously.[9] In brief, the samples were centrifuged at a speed of 1,500 revolutions per minute (rpm) for 15 min; 2 ml plasma was separated within 30 min of blood collection and stored at –25°C until analysis. For the construction of esketamine and esnorketamine calibration lines, solid substances were obtained from Parke–Davis (Dallas, Texas) and Tocris (St. Louis, Missouri), respectively.

Table 1. Target and Actual Inhalation, Infusion, and Sampling Times

Target inhalation and blood sample times	
Part 1	
Inhalation 1 (10 min)	0, 2, 4, 8, 10, 12, 14, 20, 30, 40, 70 min
Inhalation 2 (15 min)	2, 4, 8, 10, 15, 17, 19, 30, 50, 75 min
Inhalation 3 (20 min)	2, 4, 8, 10, 15, 20, 22, 24, 30, 40, 60, 80 min
Intravenous infusion (20 min)	2, 4, 8, 10, 15, 20, 22, 24, 30, 40, 60, 80, 120, 180 min
Part 2	
Inhalation 1, 2, and 3 (15 min)	0, 2, 4, 10, 15 20, 22, 24, 30, 40, 60, 80 min
Intravenous infusion (20 min)	2, 4, 10, 15 20, 22, 24, 30, 40, 60, 80 min
Actual inhalation and blood sample times	
Part 1	
Inhalation 1 for 22.0 ± 6.8 min	0, 2, 4, 10, 22 24, 26, 32, 42, 62, 82 min
Inhalation 2 for 32.9 ± 8.3 min	2, 8, 15, 33, 35, 41, 48, 63, 78, 93 min
Inhalation 3 for 41.0 ± 6.7 min	2, 8, 15, 25, 41, 43, 49, 56, 66, 81, 91, 101 min
Intravenous infusion for 20.0 ± 0 min	2, 4, 8, 10, 15, 20, 22, 24, 30, 40, 60, 80, 120, 180 min
Part 2	
Inhalation 1 for 22.0 ± 2.6 min	0, 2, 4, 10, 15, 22, 24, 26, 32, 42, 62, 82 min
Inhalation 2 for 25.4 ± 4.0 min	2, 4, 10, 15, 25, 27, 29, 35, 45, 65, 85 min
Inhalation 3 for 30.0 ± 4.2 min	2, 4, 10, 15, 30, 32, 34, 40, 50, 70, 90 min
Intravenous infusion for 20.0 ± 0 min	2, 4, 10, 15 20, 22, 24, 30, 40, 60, 80 min

Actual inhalation and infusion values are mean ± SD. The sampling times are relative to the start of inhalation.

Extraction Procedure. Ethanol 25 µl was added to all of the samples to compensate for the ethanol in the standard solution. Next, internal standard solution (25 µl nortilidine in ethanol, Parke–Davis) was added, after which the samples were mixed on a vortex shaker. Next, 100 µl of 0.1-N sodium hydroxide and a 5-ml mixture of pentane/isopropanol (95%/5%) were added. The extraction of all desired compounds was performed on a Heidolph mixer (Dijkstra Vereenigde, Lelystad, The Netherlands) by rotation at 40 rpm for 15 min. After subsequent centrifugation at 4,000 rpm for 15 min (Eppendorf 5810R Centrifuge, Boom, Meppel, The Netherlands), the organic upper layer was transferred into another tube, and the components were back extracted into 0.6 ml of 0.4-N hydrogen chloride by rotation at 40 rpm for 15 min. After another centrifugation, the organic layer was aspirated and dried in a dry block and sample concentrator (Wilten Instrumenten, Etten-Leur, The Netherlands) at 50°C under a gentle stream of nitrogen.

Analysis. After extraction, esketamine and esnorketamine data were determined by high-performance liquid chromatography on a Gemini C18 column (Phenomenex, Utrecht, The Netherlands) at 40°C. Because only the S(+)-enantiomer of ketamine was given we used a nonstereospecific assay. The mobile phase was a mixture of phosphate buffer 0.03 N:acetonitrile (92%/8%) at pH 2.25. Monitoring of the eluent was performed at 195 nm with a photodiode array detector (PDA 100, Dionex, Amsterdam, The Netherlands).

Concentrations, Precision, and Accuracy of the Assay. The linear range of the assay was 10 to 1,000 and 10 to 500 ng/ml for esketamine and esnorketamine, respectively. The day-to-day precision was 3.4%, 3.7%, and 3.4% at esketamine concentrations of 40, 200, and 1,000 ng/ml and 5.3%, 3.9%, and 3.6% at esnorketamine concentrations of 20, 100, and 500 ng/ml,

respectively. The day-to-day accuracy for esketamine was 3.2% (at 40 ng/ml), 2.2% (200 ng/ml), and –4.5% (1,000 ng/ml) and for esnorketamine 2.3% (at 20 ng/ml), 2.4% (100 ng/ml), and –2.2% (500 ng/ml). The within-day precision for esketamine was 1.7% (at 40 ng/ml), 1.5% (200 ng/ml), and 1.7% (1,000 ng/ml) and for esnorketamine 1.0% (20 ng/ml), 3.4% (100 ng/ml), and 2.2% (500 ng/ml). The within-day accuracy for esketamine was 1.9% (40 ng/ml), 3.4% (200 ng/ml), and 9.8% (1,000 ng/ml) and for esnorketamine 0.6% (20 ng/ml), –0.1% (100 ng/ml), and 7.2% (500 ng/ml). The lower limit of quantitation was 10 ng/ml; apart from baseline samples, none of the samples had esketamine or esnorketamine concentrations of less than 10 ng/ml.

Pharmacokinetic Analysis

The pharmacokinetic analysis was performed on the combined data sets of parts one and two of the study; inhalation and intravenous infusion data were analyzed simultaneously. The data were initially analyzed using the pharmacokinetic model structure as proposed by Sigtermans et al.,[9] which consists of three compartments for esketamine, three compartments for the metabolism pathway, and two compartments for esnorketamine. First, the three-compartment model was fitted to the ketamine concentration data only, under the assumption that the administration during inhalation was equivalent to an infusion in the central compartment × F (where F is a dose-independent bioavailability factor); the inhalation rate was computed by ratio of the amount of esketamine in the reservoir and the time needed to empty the reservoir. Furthermore, based on visual inspection of the data fits, which showed some nonlinearity with respect to inhaled dose and attained concentrations, it was explored if a better description would be obtained by assuming impaired absorption at higher concentrations due to the

occurrence of sedation or possibly reduced breathing activity, using an inhibitory sigmoid E_{MAX} function × inhalation rate. This function describes the concentration-dependent bioavailability of the inhalant and is characterized by the plasma concentration at which absorption was impaired by 50% and a steepness factor. In addition, it was explored if a better description of the data would be obtained by adding delay compartments between the inhalation and central compartment or a combination of a fast and slow pathway from inhalation to the central compartment.

The esnorketamine data were analyzed using the complete model structure proposed by Sigtermans *et al.*[9] but with fixed esketamine pharmacokinetic parameter values to the empirical Bayesian estimates from the best fit of the previous step (the esketamine data fit). This sequential approach of analyzing the esketamine and esnorketamine data differs from a combined data analysis mainly in that it allows a separate focus for the two types of data without one affecting the other, as is also often done in pharmacokinetic–pharmacodynamic studies. Because esnorketamine formation and the

volume of the central compartment for esnorketamine are not simultaneously identifiable, the central compartments for esketamine and esnorketamine were assumed to be equal (*i.e.*, $V_{1K} = V_{1NK}$), and the fraction F_M of esketamine that is metabolized to esnorketamine was not corrected for the slightly different molecular weights.

Statistical Analysis

In this phase one trial, we set the number of subjects to 20, which is based on previous experiences.[9] The pharmacokinetic data were analyzed using mixed-effects modeling software NONMEM version 7.3 (ICON Development Solutions, Hanover, Maryland). Random effects were included in the model allowing for assessment of between-subject variability and relative and additive residual variability. Model selection was based on visual inspection of data fits, goodness-of-fit plots, SEs of the estimated parameters, and the minimum value of the objective function. A decrease in the objective function of 6.63 for an additional model parameter was considered significant at the $P < 0.01$ level. Goodness of fit was
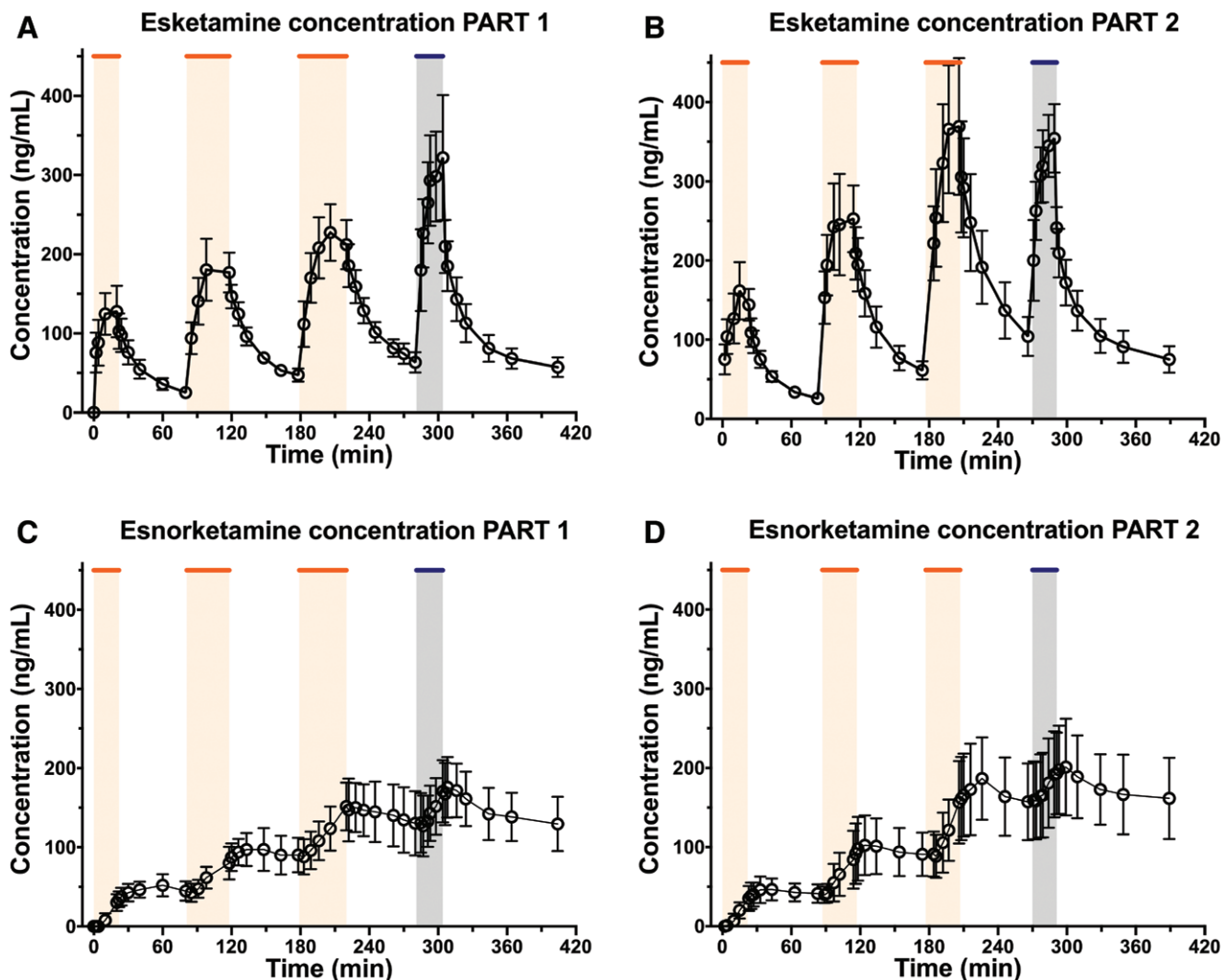

Fig. 1. Plasma ketamine (*A* and *B*) and norketamine (*C* and *D*) concentrations of part one and part two of the study. Data points are mean ± SD. The *orange bars* are the inhalation phases, *gray bars* the infusion phases.

assessed by visual inspection of the data fits, coefficient of determination,[10] plots of predicted *versus* measured concentration, individual weighted residual *versus* time, and individual weighted residual *versus* the predicted concentration. Data are reported as median ± SE of the estimate.

Normalized prediction discrepancies (NPDs) were calculated by NONMEM as a visual predictive check of the final ketamine and norketamine pharmacokinetic models.[11] In brief, 300 Monte Carlo simulations are performed, and the number of times an observation is greater than the model prediction is counted. The NPDs are the counts divided by 300, transformed *via* the inverse normal distribution. Under the null hypothesis that the model is correct, the NPDs should have a normal distribution. It was checked by visual inspection that the NPDs *versus* time showed no trends and/or heteroscedasticity.

Results

Subjects

Twenty-one subjects of either sex were recruited, of which 20 completed the protocol without unexpected side effects. One subject did not complete the study due to persistent vomiting; the data from another were lost for technical reasons. The analyses were performed on the data from 19 subjects (10 men and 9 women, aged 24 ± 2 yr for mean ± SD, and body mass index of 22 ± 2 kg/m^2), 10 who participated in part one and nine others in part two. For the pharmacokinetic analyses, the data from the two parts were combined.

Inhalation

According to the specifications of the manufacturer of the nebulizer, we expected that the aerosol production would be 0.5 ml fluid per minute. Hence, we expected inhalation times of 10, 15, and 20 min for the first, second, and third inhalations of part one, respectively, and 15 min for all three inhalations of part two. However the actual inhalation times were longer (see table 1), partly due to the slower nebulization of ketamine and partly due to the slower efficacy of inhalation by the subjects because of mild sedation. The mean (± SD) esketamine and esnorketamine concentrations in plasma are given in figure 1. The maximum plasma esketamine concentrations observed during inhalation increased dose dependently in both parts of the study and ranged from 128 to 227 ng/ml in part one and 161 to 369 ng/ml in part two. Peak esnorketamine concentrations were approximately 50% of peak esketamine concentrations.

Pharmacokinetic Analysis: Model Selection

The base model, in which inhalation was considered an infusion × F (where F is dose-independent bioavailability), had an objective function value (OFV) of 6,380. Visual inspection of the data fits showed some systematic underprediction and overprediction at low and high esketamine concentrations, respectively (data not shown). The model with an inhibitory sigmoid E_{MAX} function to describe impaired absorption at high esketamine concentrations (*i.e.*, dose-dependent bioavailability) had an OFV of 6,032 (*P* < 0.01). Although this model was able to take the nonlinearity observed with the base model into account, a small but consistent overprediction occurred for the concentrations measured
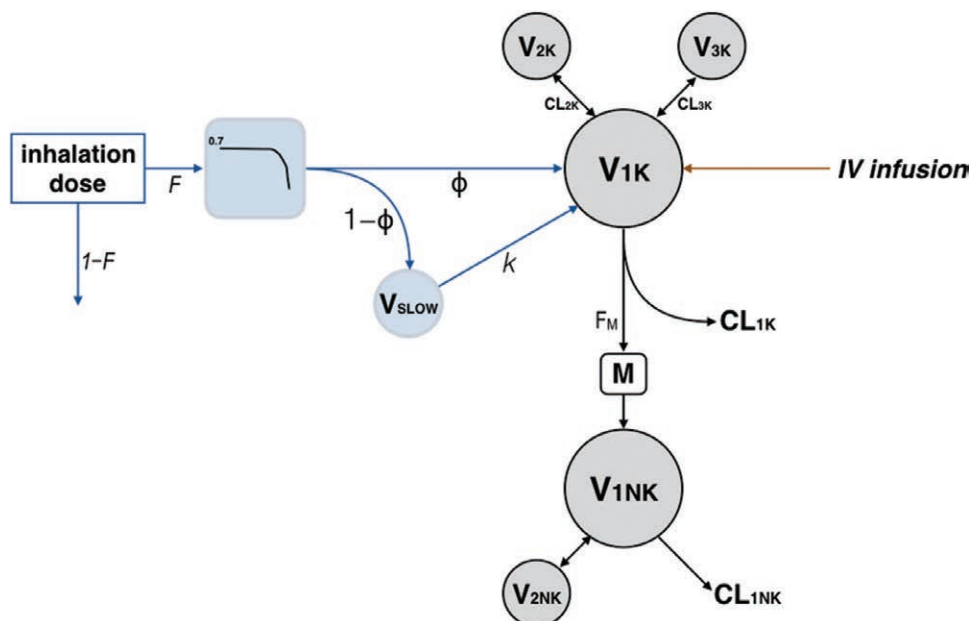

Fig. 2. Final pharmacokinetic model. F is bioavailability. V_{1K}, V_{2K}, and V_{3K} are the volumes of ketamine compartments one, two, and three; V_{2NK} is the volume of norketamine compartment two. CL_{1K} is the terminal clearance of ketamine; CL_{2K} and CL_{3K} are the intercompartmental clearances between ketamine compartments one and two and one and three, respectively. CL_{1NK} is the terminal clearance of norketamine; CL_{2NK} is the intercompartmental clearance between norketamine compartments one and two. φ is the fraction of inhaled ketamine that directly transits into the compartment V_{1K}; k is the rate constant between Vslow and V_{1K}. F_M is the fraction esketamine that is metabolized to esnorketamine. M represents the three metabolism compartments (in series).

during the intravenous administration phase (data not shown). Models with delay compartments in series with the infusion only increased the OFV. However, a model with a combination of a fast (direct) and slow (delayed) pathway from infusion to the central compartment (fig. 2) had an OFV of 5,865 ($P < 0.01$), and inspection of the data fits and goodness-of-fit plots indicated that this model adequately described the data.

Pharmacokinetic Analysis: Parameter Estimates and Model Validation

Model parameter estimates are given in table 2, and esketamine and esnorketamine data fits and goodness-of-fit plots are given in figures 3 and 4. Dose-independent esketamine bioavailability (parameter F in table 1) was 70%. Estimates of the parameters of the sigmoid E_{MAX} function (dose-dependent bioavailability) were as follows: the ketamine concentration at which the dose-dependent absorption was reduced by 50% = 416 ng/ml and steepness factor = 2.4. Combining dose-dependent and dose-independent bioavailability indicates 50% bioavailability at a plasma esketamine concentration of 275 ng/ml (fig. 5). At peak esketamine concentrations (third inhalation of part two), bioavailability of the inhalant was reduced to 38%. On average, during all three inhalation sessions, dose-dependent bioavailability was reduced by 20%.

In figure 6, the esketamine concentrations associated with the fast and slow absorption pathways are plotted (data from one subject). The plot shows that, in this subject, on average approximately 20% of ketamine traveled through the slow pathway during as well as after esketamine inhalation. In the population, 70% of esketamine was directly absorbed into the circulation from the alveoli (parameter φ in table 1 and fig. 2), whereas 30% traveled *via* the slower pathway (representing either absorption *via* the gastrointestinal tract or from pulmonary tissue, after lung uptake). The rate constant of the slow ketamine transit to V_{1K} was 0.05 min^{-1} (half-life = 13 min). Finally, from our assumptions, an estimated 78% of esketamine was metabolized to esnorketamine through three metabolism compartments.

Normalized prediction discrepancies are given in figure 7 for esketamine (panel A) and esnorketamine (panel B). The normalized prediction discrepancies show that 96.4% (esketamine) and 95.1% (esnorketamine) of the data lie within the 95% CI, an indication for the absence of model misspecifications or deficiencies.

Discussion

Traditionally ketamine (racemic and the S[+]-enantiomer) is dissolved in saline and administered intravenously or intramuscularly. However, a dozen alternative routes, such as oral, nasal, and rectal administration, have been described in the need for a less resource-consuming and more comfortable administration.[12] Inhalation of nebulized ketamine is a relatively new route of ketamine administration. In this study we aimed to explore the feasibility of esketamine inhalation in a group of young and healthy adult volunteers and developed a

Table 2. Pharmacokinetic Model Parameters

	Estimate ± SEE	ω^2 ± SEE
Esketamine		
V_{1K} (L)	7.2 ± 0.7	0.26 ± 0.18
V_{2K} (L)	22.1 ± 1.9	–
V_{3K} (L)	170.0 ± 16.0	–
CL_{1K} (L/h)	88.5 ± 4.5	0.03 ± 0.01
CL_{2K} (L/h)	213.0 ± 19.0	–
CL_{3K} (L/h)	110.0 ± 8.0	0.03 ± 0.01
F	0.70 ± 0.05	0.03 ± 0.01
φ	0.70 ± 0.03	0.26 ± 0.12
B_{50} (ng/ml)	406 ± 46	0.24 ± 0.09
γ	2.4 ± 0.7	0.6 ± 0.3
k (min^{-1})	0.05 ± 0.01	–
σ_A	–	
σ_R	0.11 ± 0.01	
Esnorketamine		
V_{2NK} (L)	83.1 ± 22.0	0.10 ± 0.06
CL_{1NK} (L/h)	57.4 ± 15.0	0.04 ± 0.02
CL_{2NK} (L/h)	416.0 ± 123.0	0.09 ± 0.05
F_M	0.78 ± 0.21	0.56 ± 0.55
MTT (h)	0.13 ± 0.01	0.06 ± 0.03
σ_A	5.0 ± 0.01	
σ_R	0.08 ± 0.01	

V_{1K}, V_{2K}, and V_{3K} are the volumes of esketamine compartments one, two, and three; V_{2NK} is the volume of esnorketamine compartment two. V_{1NK} was set to be equal to V_{1K}. Under this assumption, F_M is the fraction of esketamine metabolized to esnorketamine. CL_{1K} is the terminal clearance of esketamine; CL_{2K} and CL_{3K} are the intercompartmental clearances between esketamine compartments one and two and one and three, respectively. CL_{1NK} is the terminal clearance of esnorketamine; CL_{2NK} is the intercompartmental clearance between esnorketamine compartments one and two. F is bioavailability; φ is the fraction of inhaled esketamine that directly transits into compartment V_{1K}; B_{50} is the esketamine concentration at which the inhalation of esketamine is reduced by 50%; γ is a steepness parameter of the sigmoid function *via* which esketamine inhalation is reduced at higher esketamine concentrations; k is the rate constant between Vslow and V_{1K}; MTT is the mean transit time; σ_A is the additive within-subject variability; σ_R is the relative within-subject variability; ω^2 is the between subject variability (in the log-domain); SEE is SE of the estimate. – indicates parameter not included in the statistical analysis.

pharmacokinetic model of inhalation with special emphasis on pulmonary absorption and bioavailability.

To reduce the probability of pulmonary toxicity we used preservative-free esketamine. Some effect of direct tissue exposure by (preservative-free) ketamine could not be excluded *a priori*, however.[13] We observed no respiratory adverse events during or after esketamine inhalation. This suggests that the procedure as applied by us is without acute pulmonary toxicity, but additional studies with more prolonged exposures are necessary to come to more definite conclusions.

For both parts of the study we observed that inhalation times were longer than expected by a factor of two to three (table 1). The target inhalation times were based on the information provided by the manufacturer of the nebulizer, which stated that 0.5 ml fluid would be nebulized per minute. Our results indicate that just 0.16 to 0.25 ml esketamine nebulized per minute, with lower nebulization efficacy when nebulizing higher concentrates of esketamine (this phenomenon is independent of the reduced bioavailability at higher ketamine concentrations). We relate this to the high viscosity of esketamine; the viscosity
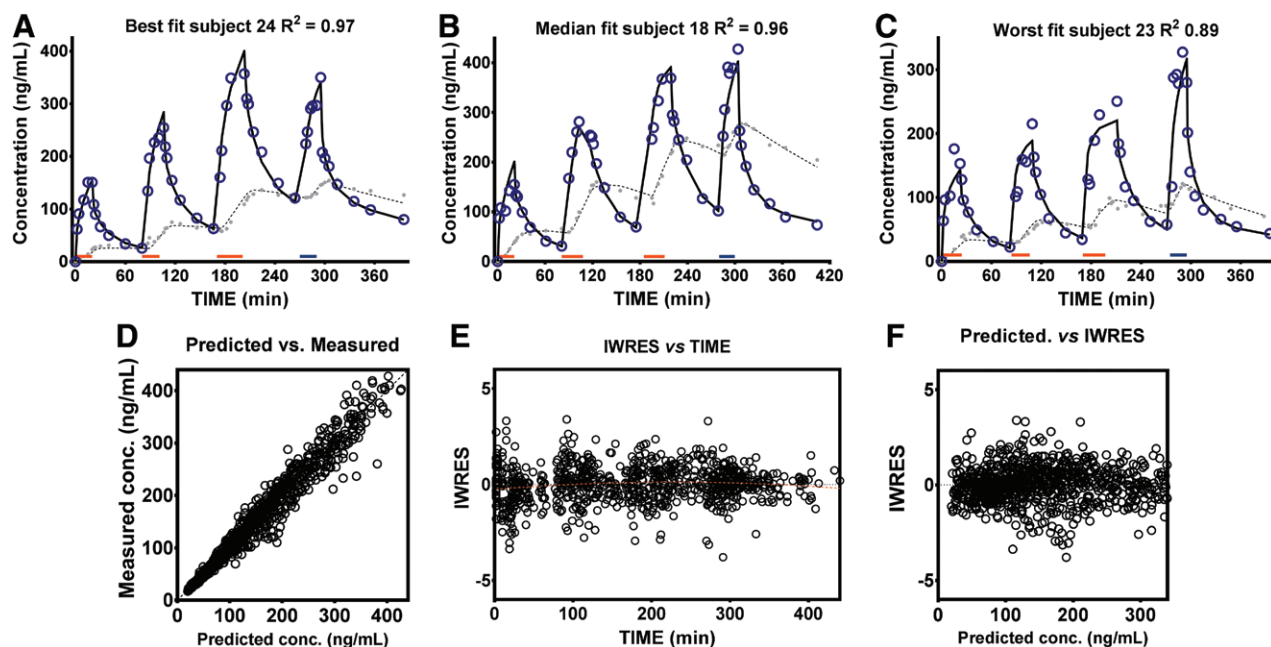
Fig. 3. Best (*A*), median (*B*), and worst (*C*) ketamine data fits based on the coefficient of determination (R^2) and goodness-of-fit plots: predicted *versus* measured concentration (conc.; *D*), individual weighted residual (IWRES) *versus* time (*E*) and individual weighted residual *versus* the predicted concentration (*F*). In *A–C*, the *blue circles* are the measured ketamine concentrations and the *black lines* the data fits; the corresponding measured norketamine concentrations (*gray dots*) and data fits (*gray lines*) are added; the *orange bars* indicate the inhalation phases, the *blue bars* the infusion phases. In *E*, to guide the eye, a smoothing curve (*red line*) was plotted through the data.
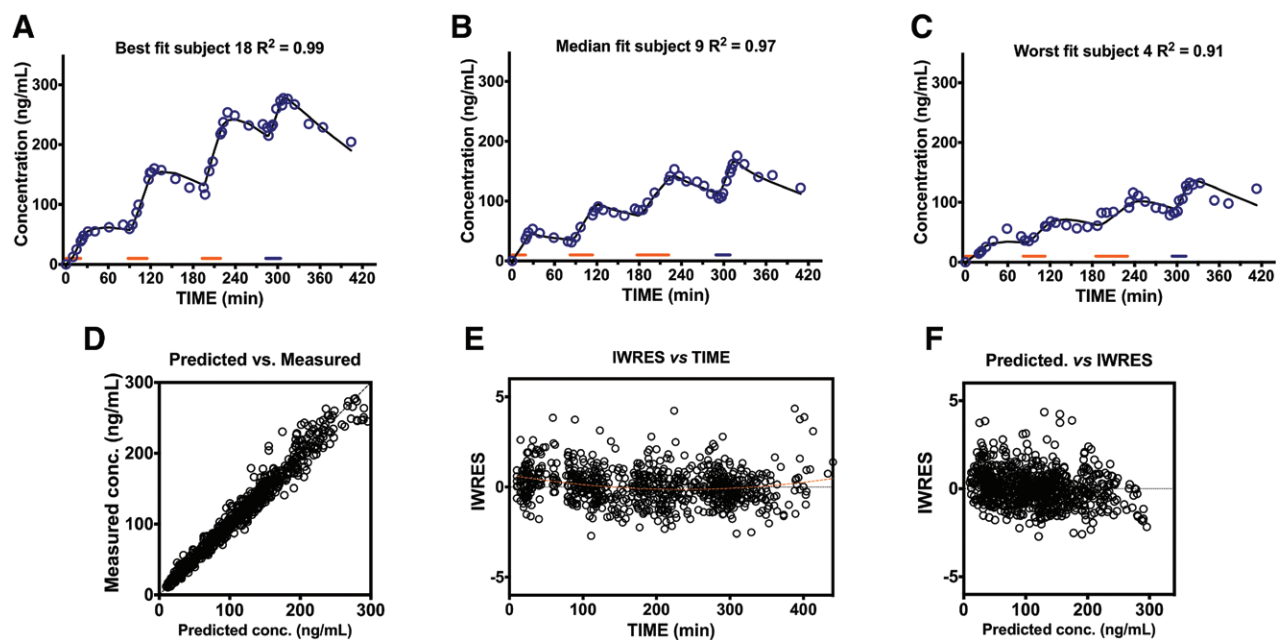

Fig. 4. Best (*A*), median (*B*), and worst (*C*) norketamine data fits as based on the coefficient of determination (R^2) and goodness-of-fit plots: predicted *versus* measured concentration (conc.; *D*), individual weighted residual (IWRES) *versus* time (*E*) and individual weighted residual *versus* the predicted concentration (*F*). The *orange* and *blue bars* in *A–C* indicate the inhalation and infusion phases, respectively. The *red line in E* is a smoothing curve.

of esketamine is three to four times greater than that of water. This is a relevant issue and should be taken into consideration when designing inhalation schemes for patient care.

Multiple absorption models of inhaled aerosolized compounds have been developed, most of which are based on the description of the fate of small liquid particles through the bronchial tree, on fluid dynamics, or a combination of the two.[14] We present a simple compartmental pharmacokinetic model that allowed for simultaneous analysis of both inhaled and intravenous esketamine.[15,16] Importantly, we were able
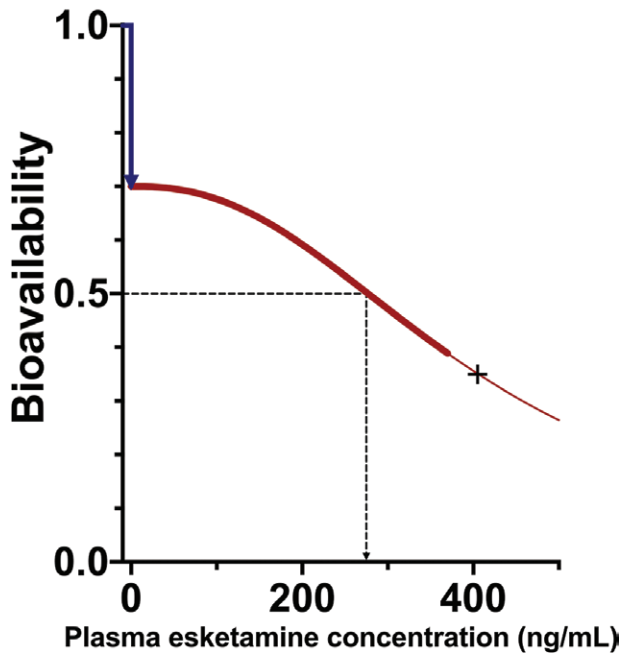
Fig. 5. The sigmoid E_{MAX} function that describes the influence of ketamine plasma concentration on the efficacy of ketamine inhalation. *Plus symbol* (+) indicates the concentration causing a 50% reduction in efficacy (B_{50}). The *blue arrow* indicates the dose-independent loss of drug; the *red line,* the dose-dependent bioavailability. The *thick part* of the *red line* indicates the average ketamine concentration range observed in the study.
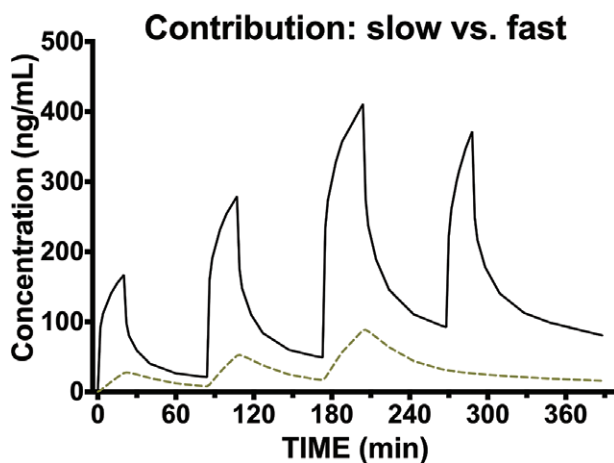

Fig. 6. The ketamine concentrations associated with the direct (or fast, *black line*) and slow (*yellow broken line*) absorption pathways of one subject.

to detect dose-independent and dose-dependent impairment of pulmonary uptake (*i.e.,* reduced bioavailability) and two distinct pulmonary absorption compartments, one rapid pathway (φ in fig. 2) that transits directly into the central compartment (V_{1K}) and one slower pathway ($1 - φ$ in fig. 2) from which ketamine is slowly released into the central compartment. Based on the objective function value, goodness-of-fit plots, and NPDs, our final model adequately described the data and was superior compared with less complex models.

Dose-independent bioavailability was 70%, indicating that 30% of the drug was lost from absorption. This may possibly be related to some quantity of liquid ketamine that remained in the container of the nebulizer or aerosolized ketamine that adhered to the mouthpiece and/or drug that was swallowed. Furthermore, it is important to realize that large inhaled aerosol particles (more than 5 μm) are mainly trapped in the oropharynx and do not reach the bronchial tree, whereas small particles (less than 1 μm) are exhaled.[14,17] As specified by the manufacturer, the size of the particles produced by the high-frequency vibrating mesh of the nebulizer ranges from 0.4 to 4.4 μm, which suggests that some of the finest esketamine particles were probably exhaled from the lungs rather than absorbed. In addition, we observed that, especially at high-plasma esketamine concentrations, after inhalation bioavailability was further reduced. This effect was modeled by a sigmoid E_{MAX} function that describes the inhalation efficacy as a function of esketamine concentration (fig. 5). The incorporation of the function optimized model fits. In particular, it abolished the overestimation of plasma concentrations at high esketamine concentrations. The dose-dependent reduced esketamine inhalation efficacy may be related to the sedative effects or respiratory depressant effects of esketamine. Sedation may cause a lesser fit of the nebulizer at the mouth and consequently the loss of aerosolized ketamine into the air. Respiratory depression may cause more of the inhalant to be deposited in the oropharynx or bronchial tree before reaching the alveoli. Additional studies are needed to investigate the importance of these two effects on esketamine inhalation.

The absorption of esketamine was best modeled by two absorption pathways, an immediate pathway and a slower pathway with a half-life of 13 min. Slow absorption phases have been described previously for various inhaled drugs, including bronchodilators and antimigraine medication.[14,16] Although the fast absorption is related to pulmonary uptake, the slow absorption may be attributed to the absorption of drug *via* the oropharynx and gastrointestinal tract or to the slow release of drug retained in pulmonary tissue that is less well perfused. In anesthetized mongrel dogs, Henthorn *et al.*[18] observed significant pulmonary uptake of the ketamine enantiomers within a small pulmonary tissue volume. Although our data do not allow for a specification of the possible absorption mechanisms, we speculate that (short-lived) uptake and release of esketamine from pulmonary tissue are responsible for the slow absorption pathway, although we cannot exclude that some esketamine was absorbed from the gastrointestinal tract. Additional studies are required to better understand the physiologic processes involved in the systemic absorption of inhaled esketamine aerosols.

The pharmacokinetic model parameter estimates of the current study are in agreement with earlier studies on intravenous esketamine.[8,19] For example, in a similar study population of healthy volunteers (mean age, 21 yr; body mass index, 21 kg/m²) and a ketamine concentration range of 10 to 500 ng/ml, estimated parameter values of the volumes of the three pharmacokinetic compartments were 8, 21, and 124 L for V_{1K}, V_{2K}, and V_{3K}, respectively, and for the clearances 80, 183, and 92 L/h for
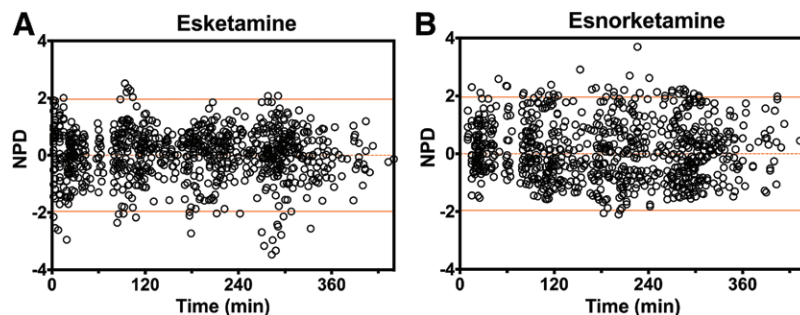
Fig. 7. Normalized prediction discrepancy (NPD) for the ketamine (*A*) and norketamine (*B*) pharmacokinetic models. The *orange lines* indicate the median value (*broken line*) ± 95% CIs (*solid lines*).

CL_{1K}, CL_{2K}, and CL_{3K}, respectively (see table 1).[19] The similarity in parameter estimates gives additional validity to the appropriateness of the pharmacokinetic model that we developed for inhaled esketamine. However, in previous studies we detected sex differences in the pharmacokinetics of esketamine, with a greater elimination clearance in women.[8] However, because the observed differences were small and not clinically relevant we opted for not assessing sex differences in the current study.

Conclusions

We successfully developed a pharmacokinetic model of esketamine inhalation. The model may serve to design inhalation regimes for patients who require esketamine treatment outside of the hospital setting. Our study did indicate, however, dose-dependent as well as dose-independent reduced bioavailability, which should be taken into account when dosing a patient.

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Competing Interests

Dr. Dahan received consultancy and speaker fees from Eurocept BV (Ankeveen, The Netherlands) in the past. The other authors declare no competing interests.

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References

1. Niesters M, Martini C, Dahan A: Ketamine for chronic pain: Risks and benefits. Br J Clin Pharmacol 2014; 77:357–67
2. Niesters M, Dahan A: Pharmacokinetic and pharmacodynamic considerations for NMDA receptor antagonists in the treatment of chronic neuropathic pain. Expert Opin Drug Metab Toxicol 2012; 8:1409–17
3. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, Tadic A, Sienaert P, Wiegand F, Manji H, Drevets WC, Van Nueten L: Intravenous esketamine in adult treatment-resistant depression: A double-blind, double-randomization, placebo-controlled study. Biol Psychiatry 2016; 80:424–31
4. Patton JS, Byron PR: Inhaling medicines: Delivering drugs to the body through the lungs. Nat Rev Drug Discov 2007; 6:67–74
5. Willson DF: Aerosolized surfactants, anti-inflammatory drugs, and analgesics. Respir Care 2015; 60:774–93
6. Ahuja V, Mitra S, Sarna R: Nebulized ketamine decreases incidence and severity of post-operative sore throat. Indian J Anaesth 2015; 59:37–42
7. Zanaty OM, El Metainy SA: A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg 2015; 121:167–71
8. Jonkman K, Duma A, Velzen M, Dahan A: Ketamine inhalation. Br J Anaesth 2017; 118:268–9
9. Sigtermans M, Dahan A, Mooren R, Bauer M, Kest B, Sarton E, Olofsen E: S(+)-ketamine effect on experimental pain and cardiac output: A population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. ANESTHESIOLOGY 2009; 111:892–903
10. Bonate PL: Pharmacokinetic-Pharmacodynamic Modeling and Simulation, 2nd edition. New York, Springer, 2011, p 16
11. Comets E, Brendel K, Mentré F: Model evaluation in nonlinear mixed effect models, with application to pharmacokinetics. J Soc Franc Stat 2010; 151:106–27
12. Kronenberg RH: Ketamine as an analgesic: Parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. J Pain Palliat Care Pharmacother 2002; 16:27–35
13. Pandey CK, Mathur N, Singh N, Chandola HC: Fulminant pulmonary edema after intramuscular ketamine. Can J Anaesth 2000; 47:894–6
14. Gaz C, Cremona G, Panunzi S, Patterson B, De Gaetano A: A geometrical approach to the PKPD modelling of inhaled bronchodilators. J Pharmacokinet Pharmacodyn 2012; 39:415–28
15. Bartels C, Looby M, Sechaud R, Kaiser G: Determination of the pharmacokinetics of glycopyrronium in the lung using a population pharmacokinetic modelling approach. Br J Clin Pharmacol 2013; 76:868–79
16. Avram MJ, Spyker DA, Henthorn TK, Cassella JV: The pharmacokinetics and bioavailability of prochlorperazine delivered as a thermally generated aerosol in a single breath to volunteers. Clin Pharmacol Ther 2009; 85:71–7
17. Chalupa DC, Morrow PE, Oberdörster G, Utell MJ, Frampton MW: Ultrafine particle deposition in subjects with asthma. Environ Health Perspect 2004; 112:879–82
18. Henthorn TK, Krejcie TC, Niemann CU, Enders-Klein C, Shanks CA, Avram MJ: Ketamine distribution described by a recirculatory pharmacokinetic model is not stereoselective. ANESTHESIOLOGY 1999; 91:1733–43
19. Olofsen E, Sigtermans M, Noppers I, Niesters M, Mooren R, Bauer M, Aarts L, Sarton E, Dahan A: The dose-dependent effect of S(+)-ketamine on cardiac output in healthy volunteers and complex regional pain syndrome type 1 chronic pain patients. Anesth Analg 2012; 115:536–46