Combined Recirculatory-compartmental Population Pharmacokinetic Modeling of Arterial and Venous Plasma S(+) and R(–) Ketamine Concentrations

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ABSTRACT

Background: The pharmacokinetics of infused drugs have been modeled without regard for recirculatory or mixing kinetics. We used a unique ketamine dataset with simultaneous arterial and venous blood sampling, during and after separate S(+) and R(–) ketamine infusions, to develop a simplified recirculatory model of arterial and venous plasma drug concentrations.

Methods: S(+) or R(–) ketamine was infused over 30 min on two occasions to 10 healthy male volunteers. Frequent, simultaneous arterial and forearm venous blood samples were obtained for up to 11 h. A multicompartmental pharmacokinetic model with front-end arterial mixing and venous blood components was developed using nonlinear mixed effects analyses.

Results: A three-compartment base pharmacokinetic model with additional arterial mixing and arm venous compartments and with shared S(+)/R(–) distribution kinetics proved superior to standard compartmental modeling approaches. Total pharmacokinetic flow was estimated to be 7.59 ± 0.36 l/min (mean ± standard error of the estimate), and S(+) and R(–) elimination clearances were 1.23 ± 0.04 and 1.06 ± 0.03 l/min, respectively. The arm-tissue link rate constant was 0.18 ± 0.01 $min^{-1,}$ and the fraction of arm blood flow estimated to exchange with arm tissue was 0.04 ± 0.01.

Conclusions: Arterial drug concentrations measured during drug infusion have two kinetically distinct components: partially or lung-mixed drug and fully mixed-recirculated drug. Front-end kinetics suggest the partially mixed concentration is proportional to the ratio of infusion rate and total pharmacokinetic flow. This simplified modeling approach could lead to more generalizable models for target-controlled infusions and improved methods for analyzing pharmacokinetic-pharmacodynamic data. **(Anesthesiology 2018; 129:260-70)**

KETAMINE is a chiral *N*-methyl-D-aspartate receptor antagonist that is available in pharmaceutical products as either the racemic mixture or as the pure S(+) enantiomer. For more than 50 yr, ketamine has been used as an anesthetic agent (alone or in combination with other agents), but in recent years there has been increasing interest in its use at much lower doses as an adjunct in the treatment of perioperative pain, chronic pain, and treatment-resistant depression.[1,2]

The pharmacokinetics of ketamine have been the subject of many investigations that have focused on clinically important aspects of pharmacokinetics, such as the differential pharmacokinetics of the R(–) and S(+) enantiomers,[3–5] pharmacokinetics during target-controlled infusion,[6] comparing the pharmacokinetics of oral *versus* IV administration,[7] and studying its pharmacokinetic-pharmacodynamic relationships for analgesic,[1] psychotropic, and cardiorespiratory effects, such as increasing cardiac output.[8,9]

Front-end kinetics are pharmacokinetic models that describe intravascular mixing by incorporating cardiac output and its distribution to characterize the oscillations of arterial and venous drug concentrations in the moments after administration as a rapid IV bolus or as a single-breath thermally generated aerosol.[10–12] Pharmacokinetic models that are able to describe front-end kinetics are multicompartmental models that yield values for intercompartmental clearances and peripheral distribution volumes that are comparable to those of standard multicompartmental models.

What We Already Know about This Topic

- Recirculatory pharmacokinetic models describe intravascular mixing by incorporating cardiac output and its distribution to characterize the oscillations of arterial and venous drug concentrations in the minutes after rapid IV drug administration
- Arterial drug concentrations during a drug infusion are higher than venous concentrations but are lower than postinfusion venous concentrations

What This Article Tells Us That Is New

- A ketamine dataset with simultaneously collected arterial and venous blood samples was used to develop an intravascular mixing model that reconciled the divergent arterial and venous concentration *versus* time relationships during and after drug infusion
- Higher arterial concentrations during drug infusion result from the contribution of both partially mixed drug from the upstream infusion and mixed recirculating drug
- The partially mixed concentration is proportional to the ratio of the drug infusion rate and cardiac output
- Higher postinfusion venous concentrations are due to contributions of drug eluting from tissue

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However, in these models the traditional single, fully mixed central compartment is a hybrid of the IV administration site, heart, pulmonary blood vessels and tissue, arterial sampling site, nondistributive blood flow, and a central venous sampling site.[13] For ketamine, such a model was used to demonstrate that the R(–) and S(+) enantiomers did not differ in their respective pulmonary uptake or peripheral tissue distribution, although their elimination clearances were different.[4]

Front-end kinetics have mostly been applied to pharmacokinetic studies with rapid drug administration followed by very frequently obtained arterial blood samples. Upton described a simplified two-compartment construct, corresponding to lung and body compartments and arterial and mixed venous drug concentrations, respectively. These concepts could be used when the drug has been administered by infusion and blood samples have been obtained relatively infrequently both during and after the infusion.[14]

In a previous study, arterial and venous blood samples were collected simultaneously during and after a 30-min ketamine infusion, once when R(–) ketamine was administered and once when S(+) ketamine was administered.[5] It was our premise that a front-end kinetic intravascular mixing model would reconcile the divergent arterial and venous ketamine concentration *versus* time curves and that the distribution kinetics of R(–) and S(+) ketamine are not different. Specifically, we postulated the higher arterial ketamine concentrations during infusion result from the contribution of both unmixed drug from the "upstream" infusion and fully mixed recirculating drug described by front-end pharmacokinetic models and that the systematically slightly higher postinfusion venous ketamine concentrations can be modeled with a contribution of higher drug concentrations eluting from arm tissue. Thus, the purpose of the current study was to build a pharmacokinetic model that incorporated arterial and venous S(+) and R(–) ketamine concentration data.

Materials and Methods

Study Details

As described previously,[5] 10 healthy male subjects aged 24 to 62 yr, weighing 68 to 92 kg, were administered approximately 7 mg of S(+) or R(–) ketamine hydrochloride *via* a 30-min constant rate IV infusion on two occasions at least 3 days apart. The relative uniformity of the subjects is an asset for model development, but limits the ability to extend the results of a "population" analysis beyond healthy, awake adult males. Doses were corrected after measuring the concentration of each dose solution. Radial artery and arm vein samples were drawn at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 120, 180, and 300 min after the start of the S(+) ketamine infusion and at 0, 5, 10, 15, 20, 25, 30, 36, 43, 50, 180, 300, and 420 min after the start of the R(–) ketamine infusion. The minor difference in sampling schedules between the enantiomers was designed to allow estimation of the prolonged elimination half-life of R(–) ketamine while keeping the number of samples the same on both occasions. The arterial line was then removed, and at 540 and 660 min, only venous samples were obtained. An enantioselective high-performance liquid chromatography assay with a lower limit of quantitation of 2 ng/ml (day-to-day coefficient of variation of 4.1 to 8.5%) was used to measure plasma S(+) and R(–) ketamine concentrations.[15]

Pharmacokinetic Data Analysis

Compartmental models were fitted independently to the R(–) and S(+) ketamine concentration *versus* time data for the venous and arterial sampling sites. The base pharmacokinetic model was then extended to test the hypotheses that independent models (with many parameters) are superior to reduced (minimal) models in which the distribution volumes and intercompartmental clearances of R(–) and S(+) ketamine are the same and that the differences between simultaneous arterial and arm venous ketamine concentrations can be accounted for by a front-end pharmacokinetic model combined with a variant of the antecubital model suggested by Levitt.[16]

Reduction of the Bayesian information criterion determined selection of the superior models described: independent, reduced, and front-end. We used the Bayesian information criterion for model selection as it places a heavier penalty on additional parameters.[17]

Front-end pharmacokinetic models are characterized by central (venous) drug input (bolus or infusion) with transfer *via* tanks-in-series delay elements, which characterize pulmonary transit and pulmonary tissue distribution, to the central (arterial) sampling compartment and further transfer from the central (arterial) sampling compartment out of the body by elimination clearance and to peripheral (tissue) compartments by intercompartmental clearance(s).[18,19] The sum of the clearances (ΣCl) from arterial blood is equal to cardiac output corrected for erythrocyte to plasma drug partitioning (*e.g.*, 0 for indocyanine green and 1.37 for ketamine in canines). Correction of blood flow within pharmacokinetic models to account for drug partitioning into erythrocytes (*i.e.*, pharmacokinetic flow) was introduced by Stec *et al.*[20] to reconcile the estimates of pharmacokinetic clearances of various drugs with independently measured blood flow. The

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first-pass arterial sum of clearances equals total plasma flow for indocyanine green (which does not partition into erythrocytes), equals cardiac output for antipyrine (which has a erythrocyte/plasma partition ratio of unity), and is more than cardiac output for drugs that partition into erythrocytes, such as ketamine, because the flow of erythrocytes is overweighted. The sum of clearances from the unmixed arterial compartment estimates cardiac output after correction for hematocrit and erythrocyte/plasma partitioning.

For a bolus input and nearly continuous arterial sampling, a model in which the central (pulmonary) mixing kinetics are fully characterized has been required to fully describe the oscillating arterial drug concentrations.[4] Upton demonstrated how a simplified version of a recirculatory model could be used to explain arterial to venous drug concentration differences during an infusion.[14] Specifically, see his equation:

$$V_{lung} * dC_a / dt = R_0 - CO * (C_a - C_C) \quad (1)$$

where V_{lung} is the arterial (only) mixing compartment, dC_a/dt is change in arterial concentration divided by change in time, C_C is mixed venous or central compartment drug concentration, CO is cardiac output or total pharmacokinetic flow (ΣCl) for drugs with an erythrocyte/plasma partition ratio different than unity, and R_0 is the drug infusion rate. At steady-state, we have:

$$C_a = R_0 / \Sigma Cl + C_C \quad (2)$$

For a prolonged infusion (*e.g.*, 30 min in the current study) and a sampling schedule with several minutes between samples, a simplified, steady-state assumption can be invoked for the central mixing (front-end) kinetics as the half-life of this process is approximately 15 s, *i.e.*, the steady-state concentration of first-pass (unmixed) drug is equal to the ratio $R_0/\Sigma Cl$.

Pharmacokinetic models of arm vein drug concentration data are based on observations that most of the forearm circulation functions as a pharmacokinetic shunt *via* skin capillaries and arteriovenous anastomoses that serve to regulate body heat by either maximizing or restricting radiation.[16] Only a fraction of the forearm circulation exchanges solutes (*e.g.*, drug) with skeletal muscle or other tissue. Thus, the capillaries of the arm are mostly a mixing compartment analogous to the arterial mixing compartment described above. If the ratio of arm arterial blood flow to total arm blood volume (mostly residing in small vessels such as capillaries) is similar to the ratio for the rest of the body, then arm vein drug concentrations should approximate mixed venous or central drug concentration.

Therefore, to relate arm vein blood drug concentrations to the mammillary model, we assume that arm vein drug concentrations (C_V) are equal to the drug concentration in the arm tissue compartment (C_{arm}) times the fraction (F) of arm blood flow that is exchanging (nonshunted) plus central compartment concentrations (C_C) times the fraction (1 – F) of arm blood flow that is not exchanging (shunted):

$$C_V = C_{arm} * F + C_C * (1 - F) \quad (3)$$

Arm vein drug concentration pharmacokinetics were modeled using a method similar to an effect compartment link model in which no drug is transferred from the drug disposition model to the arm compartment. We used a rate constant that is similar to the familiar effect compartment link. In order to account for drug partitioning between blood and the arm (*i.e.*, skeletal muscle) compartment, we added a tissue to blood partition coefficient (PC_{arm}) to equation 3:

$$C_V = C_{arm} * F * PC_{arm} + C_C * (1 - F) \quad (4)$$

where PC_{arm} was fitted as a separate structural parameter or set equal to volume of compartment 2/volume of the central compartment in order to calculate actual peripheral tissue concentration instead of plasma-apparent peripheral tissue concentration.

The extension of the base pharmacokinetic model (fig. 1) for arterial drug concentrations is described by drug input into an unmixed first-pass volume (central/pulmonary circulation), from which it is transferred by cardiac output to the mixed central compartment of a mammillary pharmacokinetic model. Observed arterial drug concentrations are fitted to the sum of the estimated drug concentrations of the central compartment and the unmixed first-pass volume, which is set to 1 l because it cannot be estimated with infrequent sampling, and cardiac output (*i.e.*, ΣCl) is an estimated parameter of the model in the manner described by Upton.[14] Equation 2 suggests that ΣCl is fully identifiable if venous drug concentrations approximate mixed venous or central compartment drug concentrations and in cases in which the fraction of arm blood flow that is exchanging (nonshunted) and tissue to blood partition coefficient are well estimated.

Mean residence time (MRT) can be expressed as the ratio of steady-state volume of distribution (V_{SS}) and elimination clearance (Cl_e):

$$MRT = V_{SS}/Cl_e \quad (5)$$

Plusquellec and Houin[21] derived the mean residence time for individual compartments. The mean residence time of the central compartment of a mammillary model (MRT_C) is equal to the reciprocal of the elimination rate constant (k_{10}):

$$MRT_C = 1/k_{10} \quad (6)$$

Starting with the equality of MRTs for the S(+) and R(-) enantiomers ($MRT_{C,S[+]}$ and $MRT_{C,R[-]}$), a correction can be derived when the components of MRT (*i.e.*, the rate elimination constants $k_{10,S[+]}$ and $k_{10,R[-]}$) are not equal.

$$MRT_{C,S(+)} = MRT_{C,R(-)} \quad (7)$$

then

$$1/k_{10,S(+)} = 1/k_{10,R(-)} \quad (8)$$

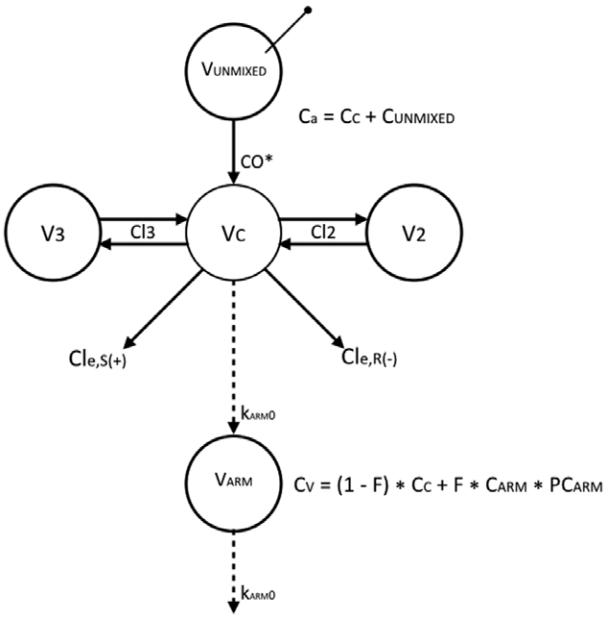

Fig. 1. Final compartmental model used to fit arterial and venous data. Drug is infused into the unmixed compartment ($V_{unmixed}$; *line topped with circle*) from which it is cleared by pharmacokinetic flow (CO* – cardiac output corrected for red blood cell:plasma partitioning and hematocrit) to the central compartment (V_C) of a three-compartment model with rapidly and slowly equilibrating peripheral compartments V_2 and V_3, intercompartmental clearances Cl_2 and Cl_3, and elimination clearances $Cl_{e,S(+)}$ and $Cl_{e,R(-)}$ for the respective enantiomers. The *dashed lines*, k_{arm0}, represent the link rate constant into and out of the arm compartment (V_{arm}). Arterial ketamine concentrations (C_a) are modeled as the sum of the concentrations C_C and concentration of the unmixed compartment ($C_{unmixed}$) and venous ketamine concentrations (C_v) are modeled as the sum of C_C times (1 – F) and the fraction of arm blood flow to arm tissue (F) times the concentration of the arm tissue compartment (C_{arm}) times the partition coefficient for the arm (P_{Carm}) tissue (equation 4).

Multiplying both sides of the equation by the respective enantiomeric ratio of central compartment volumes (V_C/V_C), matching the respective enantiomeric k_{10}s, and rearranging yields:

$$V_{C,S(+)} = V_{C,R(-)} * Cl_{e,S(+)}/Cl_{e,R(-)} \quad (9)$$

Thus, even when it can be demonstrated that S(+) and R(–) ketamine distribute to peripheral tissues by similar mechanisms, the respective central compartments will vary according to their elimination rate constants or elimination clearances (Cl_es), according to the relationship in equation 9. This relationship was used to reconcile otherwise different estimates for the central compartment volumes of the R(–) and S(+) enantiomers in the combined models.

Statistical Analysis

Data analysis was performed with Phoenix 64 NMLE 7.0 using the FOCE ELS algorithm (Certara, USA). Model parameters were assumed to be log-normally distributed across the population. Residual error was calculated as relative error. Model parsimony of nested models was determined by a decrease in the Bayesian information criterion. Interoccasion variability was modeled as an additional source of interindividual variability according to the equation

$$\theta_j = \theta_{TV} * exp(\eta_j + \eta_{occasion}) \quad (10)$$

where θ_{TV} is a population typical value (mean) for a pharmacokinetic parameter and θ_j is the individual parameter estimate of the jth subject, η_j (eta) is a random variable describing the variance between the individual (θ_j) and the population mean (θ_{TV}) estimates, and $\eta_{occasion}$ is the random variable describing the variance between estimates between the separate occasions on which the S(+) and R(–) entaniomers were administered to an individual.

The inclusion of interoccasion variability on particular parameters was conducted in the stepwise manner of including potential covariates.[22] In this case, from the base model, an interoccasion eta (η) was tested in a stepwise forward inclusion process. The minimal criterion for inclusion was a reduction in the –2 log likelihood at the $P < 0.01$ level or at least 6.63 points. Backward elimination of these parameters was set at $P < 0.001$ or an increase in –2 log likelihood of 10.83.

Ketamine concentrations below the lower limit of quantitation (*i.e.*, less than 2 ng/ml) were censored in the same manner as was done for the previous noncompartmental analyses of these data.[5] For comparison, the M3 method of Beal[23] for including data outside the limits of quantitation was conducted on the final model.

A visual predictive check was performed by using the final model parameter estimates to simulate data for 1,000 virtual subjects and calculating their fifth, fiftieth, and ninety-fifth percentiles at all sampling times. The distributions of the simulated ketamine concentrations were visually compared with the measured concentrations at each sampling time.

Results

As previously reported,[5] except for age, the 10 male subjects were quite homogeneous, with a mean ± SD age of 32 ± 11 yr and a mean weight of 75.6 ± 7.5 kg, and they received 7.1 ± 0.3 mg R(–) and 7.1 ± 0.5 mg S(+) ketamine hydrochloride on the two respective occasions.

Observed S(+) and R(–) arterial and venous ketamine concentrations *versus* time relationships are illustrated in figure 2, A and B. During the respective infusions of S(+) and R(–) ketamine, the arterial drug concentrations were systematically higher than the venous drug concentrations, while the venous drug concentrations became systematically higher shortly after the infusions were stopped. Despite similar S(+) and R(–) ketamine doses, R(–) ketamine concentrations remained above the lower limit of quantitation longer, indicating the relatively smaller elimination clearance.

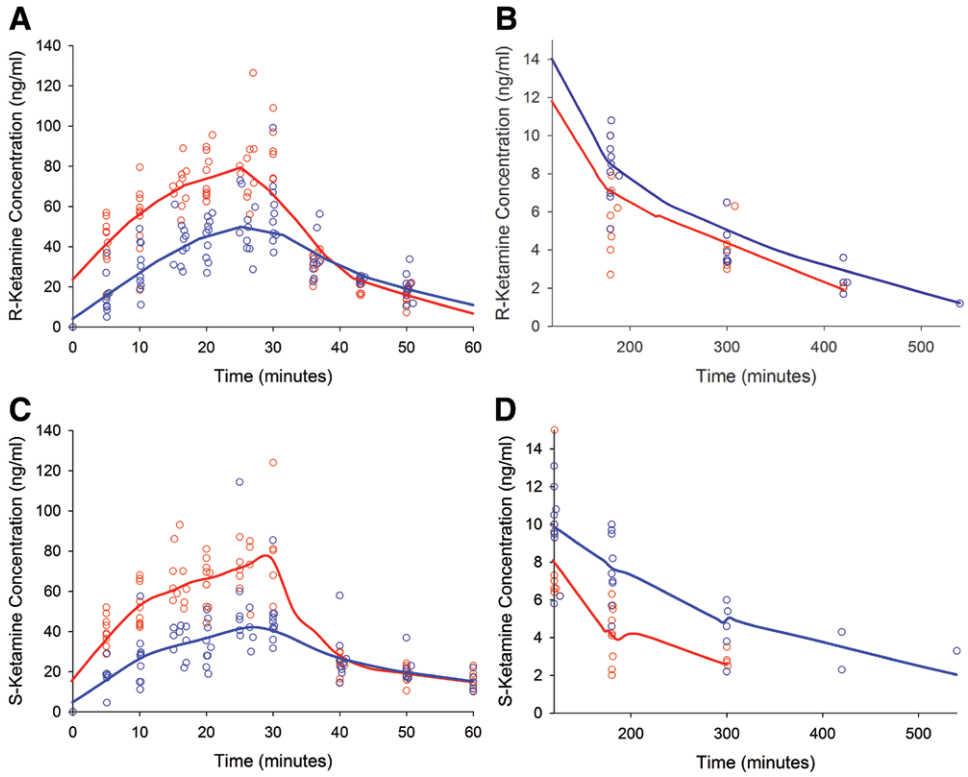

Fig. 2. (*A* and *B*) Observed S(+) ketamine concentrations for arterial (*red open circles*) and venous (*blue open circles*) sampling. Locally weighted scatterplot smoothing (lowess) plots with *red lines* for arterial and *blue lines* for venous for (*A*) the first 60 min and (*B*) minutes 120 to 540. (*C* and *D*) Observed R(–) ketamine concentrations for arterial (*red open circles*) and venous (*blue open circles*) sampling. Locally weighted scatterplot smoothing (lowess) plots with *red lines* for arterial and *blue lines* for venous for (*C*) the first 60 min and (*D*) minutes 120 to 540. Note that concentration scales for (*A*) *versus* (*B*) and (*C*) *versus* (*D*) are tenfold different.

Model building and testing are summarized in table 1. Following conventional modeling approaches, data were first fit to four independent two-compartment models for the arterial and venous ketamine concentration *versus* time data for both S(+) and R(–) ketamine. This 33-parameter model (*i.e.*, 16 thetas, 16 etas, and 1 residual error parameter) resulted in an Akaike information criterion of 2,816 and a Bayesian information criterion of 2,950. A similar three-compartmental approach with 49 parameters resulted in a Bayesian information criterion of 3,040, thus favoring the two-compartment model when each set of samples (*i.e.*, S(+) and R(–) with arterial and venous samples) is modeled independently.

Using the assumption from previous analyses that S(+) and R(–) ketamine distribute to the same volumes and have the same intercompartmental clearances,[4] reduced two- and three-compartmental models with 21 and 29 parameters, respectively, resulted in Bayesian information criteria of 2,934 and 2,935, respectively, making this reduced model, based on similar distribution kinetics for S(+) and R(–) ketamine, superior to the models in which S(+) and R(–) were modeled independently.

Table 1. Results of the Model Fitting and Selection Process

	AIC	BIC	No. Parameters
Two-compartment independent R(+) and S(–) distribution without A-V model	2,816	2,950	33
Three-compartment independent R(+) and S(–) distribution without A-V model	2,841	3,040	49
Two-compartment linked R(+) and S(–) distribution without A-V model	2,849	2,934	21
Three-compartment linked R(+) and S(–) distribution without A-V model	2,818	2,935	29
Two-compartment linked R(+) and S(–) distribution with A (mix) – V (arm) model	2,895	2,964	17
Three-compartment linked R(+) and S(–) distribution with A (mix) – V (arm) model	2,844	2,929	21

The results move from standard independent models at the top to one in which the distribution kinetics of S(+) and R(–) ketamine are modeled as being equal (middle two) to one in which the distribution kinetics of S(+) and R(–) ketamine are modeled as being equal in addition to modeling arterial and venous (A-V) ketamine concentration differences. No. parameters = total number of parameters in the model(s) used to fit the four different datasets from each individual (*i.e.*, arterial S(+) ketamine, arterial R(–) ketamine, venous S(+) ketamine, and venous R(–) ketamine).

AIC = Akaike information criterion; BIC = Bayesian information criterion.

A model, incorporating arterial and venous ketamine concentrations into one with arterial mixing and arm vein compartments and expressing the tissue to plasma partition ratio (*i.e.*, PC_{arm} in equation 4) as volume of compartment 2/volume of the central compartment, resulted in two- and three-compartment models with 17 and 21 parameters, respectively, and Bayesian information criteria of 2,964 and 2,929, respectively, making the model based on front-end arterial mixing and an arm vein compartment superior to the models in which S(+) and R(–) were modeled independently or combined and modeled arterial and venous drug concentrations separately. The relatively poor performance of the two-compartment version of this model, whether using either Akaike or Bayesian information criteria, likely relates to the assumption that the partition coefficient between the plasma ketamine concentration and the arm tissue ketamine concentration (PC_{arm}) is equated to volume of compartment 2/volume of the central compartment. Thus, for this reduced arterial and venous drug concentration model, only the three-compartment model had an improved Bayesian information criterion (*i.e.*, 2,929) *versus* all of the other models.

From the final model, etas with very small distributions were sequentially removed from the model until the Akaike information criterion did not decrease and the standard error of all parameter estimates could be calculated. This model had 17 parameters and an Akaike information criterion of 2,838. See Supplemental Digital Content, http://links.lww.com/ALN/B718.

The combination of small dose (7 mg) and a long sampling schedule put several ketamine concentrations at later time points beyond the lower limit of quantitation. Censoring these data *versus* analyzing them with the M3 method of Beal[23] did not affect the parameter estimates of central compartment or ΣCl, but did have small effects on the volume of compartment 3 and elimination clearance. Caution should be exercised in extending predictions from this model beyond the limits of the data (*i.e.*, beyond approximately 300 min from start of the infusion).

Finally, the parameters of the last reduced three-compartment, 17-parameter model was tested to determine if interoccasion variability (same subjects studied several days apart) of the model parameters with etas would improve the fit. No parameters were significantly improved by including interoccasion variability (equation 8). All interoccasion eta parameter inclusion made negligible differences, and none even met a "relaxed" $P < 0.05$ criterion for inclusion; the "best" parameter considered for inclusion was total pharmacokinetic flow.

The pharmacokinetic parameter values are given in table 2 along with omega standard errors. Of note, the typical value of elimination clearance of the S(+) enantiomer was 16% more than the clearance for R(–) (1.23 ± 0.04 *vs.* 1.06 ± 0.03 l/min, respectively, mean ± standard error of the estimate). The fractional contribution of the arm compartment ketamine concentrations to arm vein blood concentrations was 0.04 ± 0.01 and the estimated typical total pharmacokinetic flow was 7.59 ± 0.36 l/min. The fixed effects parameters of the base mammillary model and the total pharmacokinetic flow for the front-end mixing model were well estimated, with no coefficient of variation above 10%.

Table 2. Results for the Final Model

	Typical Value ± SEE	ω^2 ± SEE
V_C (l)	44.93 ± 1.79	0.09 ± 0.009
V_2 (l)	136.58 ± 5.95	*
V_3 (l)	377.97 ± 20.91	*
Cl_2 (l/min)	3.17 ± 0.14	*
Cl_3 (l/min)	0.65 ± 0.03	*
$Cl_{eS(+)}$ (l/min)	1.23 ± 0.04	0.08 ± 0.008
$Cl_{eR(-)}$ (l/min)	1.06 ± 0.03	0.09 ± 0.010
k_{arm0} (min^{-1})	0.18 ± 0.01	*
Pharmacokinetic flow (l/min)	7.59 ± 0.36	0.09 ± 0.009
$V_{unmixed}$ (l)	1	
F	0.04 ± 0.01	0.69 ± 0.07
δ^2	0.24 ± 0.02	*

The final model has a front-end mixing compartment, characterized by an estimated pharmacokinetic flow term and an arm compartment, characterized by an exchange rate constant and a fractional contribution of arm compartment concentration to venous drug concentration.

*Parameter fixed to zero.

δ^2 = Intrasubject variability; ω^2 = intersubject variability; Cl_2 and Cl_3 = intercompartmental clearance between the central compartment (V_C) and the rapidly and slowly equilibrating compartments, V_2 and V_3, respectively; Cl_e = elimination clearances for S(+) or R(-) ketamine, respectively; F = fraction of venous ketamine concentration contributed by arm tissue ketamine concentration; k_{arm0} = venous arm compartment rate constant; SEE = standard error of the estimate; $V_{unmixed}$ = volume of the unmixed compartment fixed at a value of 1.0.

The analysis using the M3 method of Beal[23] for samples below the lower limit of quantitation did not affect front-end estimates as all of the relevant ketamine concentrations were well above the lower limit of quantitation. However, small differences were observed for the estimates of steady-state volume of distribution (mainly volume of compartment 3) and the elimination clearances. We have not reported those results as they were not central to the primary aim of the study and to allow direct comparison with the previous noncompartmental analysis of these data.[5]

The observed *versus* final *post hoc* individual model predictions for arterial and venous S(+) and R(–) ketamine concentration *versus* time curves are presented in figure 3. The conditional weighted residuals *versus* time relationships are presented in figure 4. The visual predictive checks were performed as described and are presented in figure 5.

Discussion

The aim of the current study was to fit both arterial and venous concentration *versus* time data to a single pharmacokinetic model that has a mixing (front-end) compartment with a clearance equal to total pharmacokinetic flow and S(+) and R(–) ketamine distribution volumes and intercompartmental clearances that are not different. Differences between arm venous and arterial drug concentrations were further explored by incorporating physiologically based

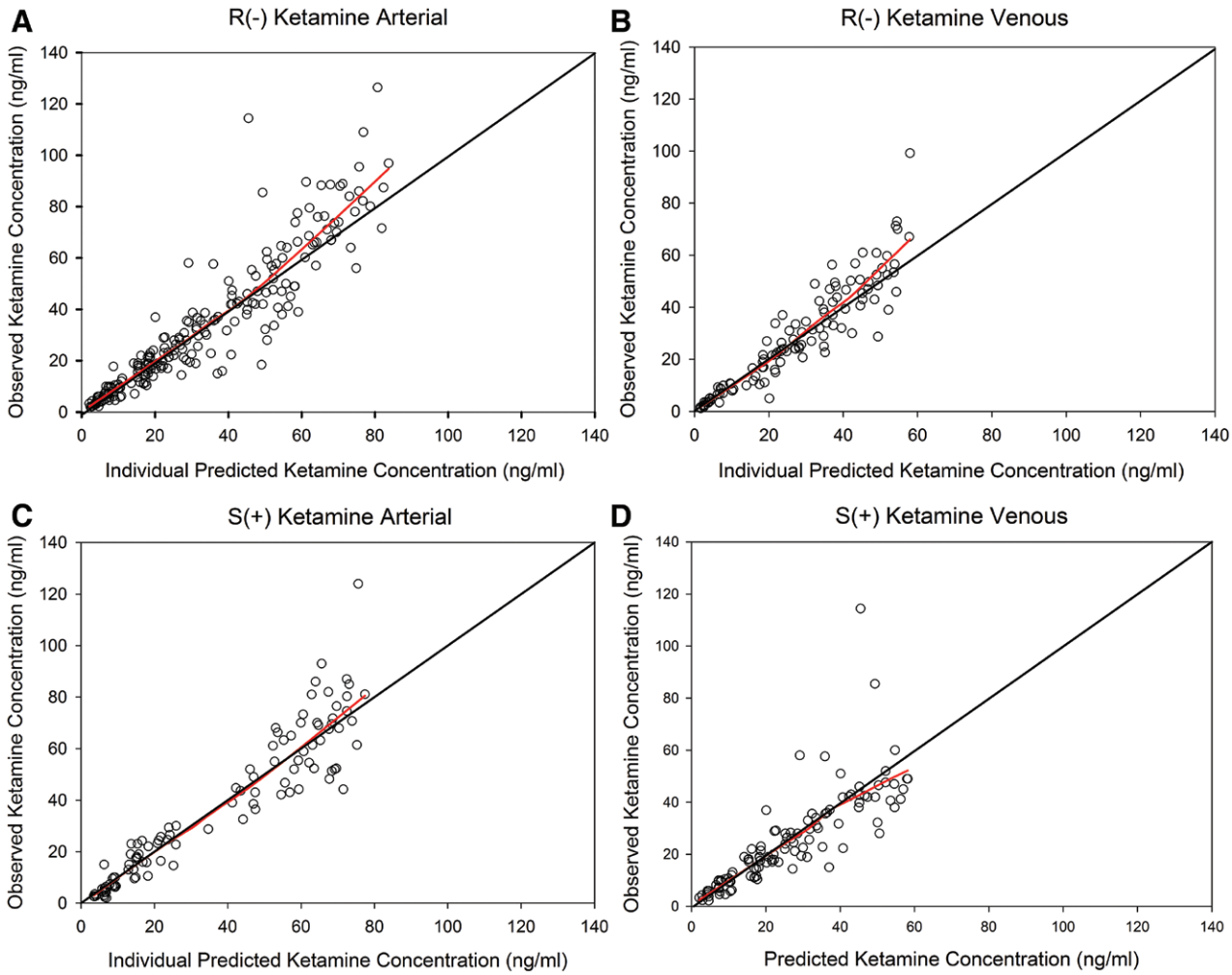

Fig. 3. Observed (*open circles*) *versus* predicted ketamine concentrations for the *post hoc* individual models of S(+) arterial (*A*) and venous (*B*) and R(–) arterial (*C*) and venous (*D*) concentrations. The lines of identity are the *black lines*, and the locally weighted scatterplot smoothing (lowess) lines are *red*.

pharmacokinetic modeling techniques described by Levitt[16] into a compartmental modeling structure.

Recirculatory pharmacokinetic models were developed from studies that used an instantaneous central venous injection and rapid arterial blood sampling. Total pharmacokinetic flow was determined by dividing drug dose by area under the first-pass drug concentration *versus* time curve (*i.e.*, prerecirculation of mixed drug). This approach has been employed by several investigators to assess the influence of cardiac output and its distribution to tissues on the pharmacokinetics and pharmacodynamics of drugs.[12,18,24–28]

These recirculatory concepts have not been widely used in data analyses of longer infusions or target-controlled infusions.[29] Upton suggested that during drug infusion arterial blood contains drug that has only mixed within a "lung compartment," since the arterial sampling site is in this sense downstream from the infusion.[14] A simple steady-state equation was suggested in which the partially mixed arterial blood drug concentration is simply the infusion rate/ΣCl (equation 2). Thus, during constant or target-controlled infusions, arterial drug concentrations could be quite sensitive to cardiac output since ΣCl is proportional to cardiac output. This sensitivity would be greatest for drugs with high elimination clearances (*e.g.*, ketamine, sufentanil) and least for drugs with a low elimination clearance (*e.g.*, alfentanil) because the effect of cardiac output on arterial drug concentration during infusion is approximately the same for all drugs and the effect of elimination clearance on arterial drug concentrations during infusion varies with the drug.

By extension, context sensitive half-time,[30] determined from arterial drug concentration data, would also be sensitive to cardiac output as the unmixed infusion contribution (equation 2) largely disappears within a minute regardless of cardiac output. Thus, low cardiac output states, in which the magnitude of the mixing artifact is greatest, will have much shorter apparent half-times. This effect on context sensitive half-time was observed in a pharmacokinetic study of sufentanil in pigs in which cardiac output was adjusted to low, medium, and high values.[31]

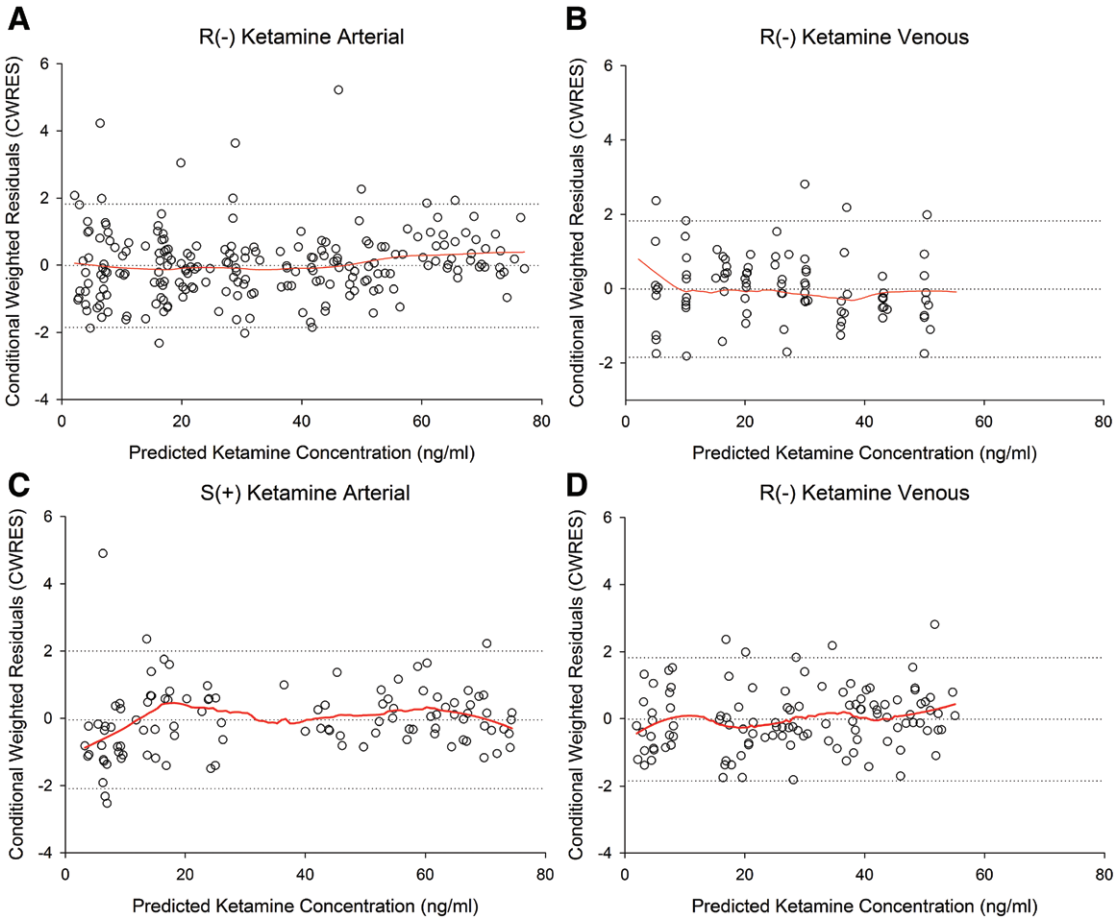

Fig. 4. Conditional weighted residual (CWRES) *versus* time and conditional weighted residual *versus* the predicted concentrations for arterial R(–) and S(+) ketamine concentrations (*A*), venous R(–) ketamine concentrations (*B*), arterial ketamine concentrations (*C*), and venous S(+) ketamine concentrations (*D*). *Red lines* are locally weighted scatterplot smoothing at the fiftieth percentile.

The estimated typical value for pharmacokinetic flow in this analysis was 7.6 l/min. To correct this estimate of pharmacokinetic flow[20] to blood flow would require erythrocyte to plasma partitioning data and hematocrit. These data are not available. Assuming a erythrocyte-to-plasma partition ratio similar to the canine value of 1.4[4] and a hematocrit of 0.45, the "true" typical cardiac output in these subjects is 6.5 l/min and within the physiologic range for healthy men. These values are consistent with our assumption that venous plasma ketamine concentrations more closely resemble mixed central compartment ketamine concentrations than arterial plasma drug concentrations during an infusion.

In the current analysis, arm vein samples were considered to be mixed and to have a small contribution from drug exchange with arm tissue. It was postulated that a total pharmacokinetic flow parameter could reconcile the large arterial to venous concentration differences during infusion, and the link compartment could reconcile the small arterial to venous concentration differences seen after the infusion.

Olofsen *et al.* have previously modeled simultaneously obtained arterial and venous morphine-6-glucuronide concentrations.[32] They had also noted arterial concentrations were initially higher and subsequently lower than venous morphine-6-glucuronide concentrations. Their model characterized the arterial and venous data well, resulting in a morphine-6-glucuronide structural model that also has 10 structural parameters.

Postinfusion venous blood ketamine concentrations were systematically higher than the corresponding arterial ketamine concentrations (fig. 2). Levitt postulated that antecubital venous blood is also subject to downstream mixing components in the form of distribution of drug to and from tissue (mainly skeletal muscle).[16] Using a physiologically based pharmacokinetic model in which a large proportion of arm blood flow serves capillaries excluded from drug exchange (flowing mainly to skin for temperature regulation), he was able to account for the arterial to venous ketamine concentration differences after infusion from the current data[5] using extracted values from the figures for mean data. In the current work, Levitt's approach was incorporated into a population mammillary pharmacokinetic model of the complete dataset. The compartmental model estimate of the tissue contribution to venous ketamine concentrations (0.04) is consistent with the physiologically based

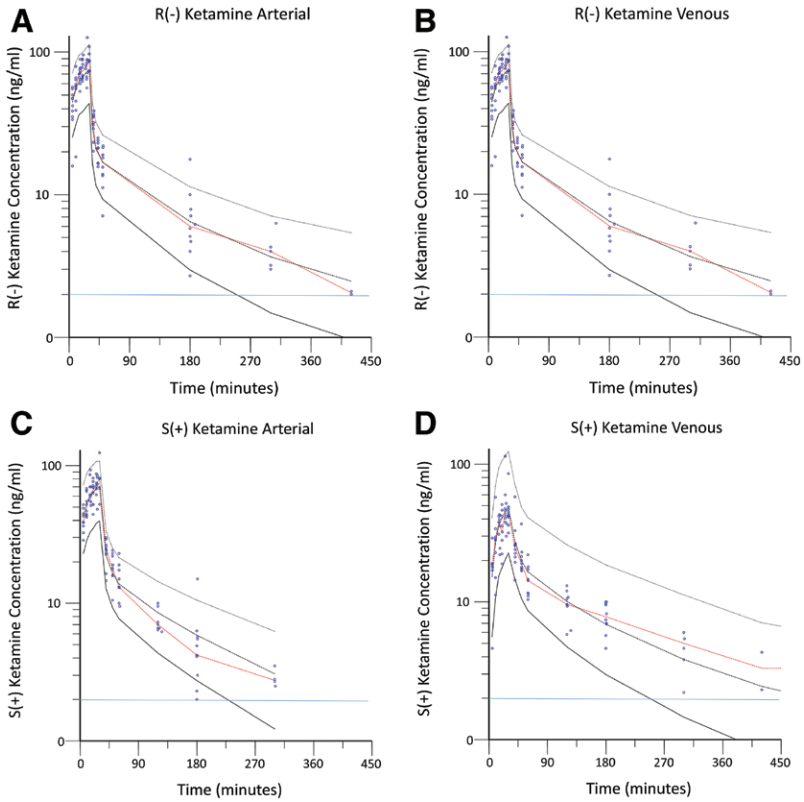

Fig. 5. Visual predictive check. The *blue circles* represent the observed data for S(+) ketamine (arterial and venous) and R(–) ketamine (arterial and venous), respectively; the *red line* represents the 50% of the observed concentrations at each time point; and the *black lines* represent the ninety-fifth, fiftieth, and fifth percentiles of the simulated concentrations at each time point. The *light blue line* is at the lower limit of quantitation for the assay (2 ng/ml).

pharmacokinetic model estimate from the mean ketamine concentration values. Levitt estimated that the fraction of arm blood flow perfusing skeletal muscle was 0.05. In addition, Levitt used tissue to plasma partition ratios for muscle, adipose, and "other" tissues of 2, 10, and 4, respectively. The current estimate of PC_{arm} (volume of compartment 2/volume of the central compartment) of 3.04 is within the expected range for muscle and other tissue, while volume of compartment 3/volume of the central compartment (8.4) more closely resembles his estimate for adipose tissue.

Figure 6 presents a simulation of predicted concentrations after a 7 mg S(+)-ketamine hydrochloride dose infused at a constant rate over 30 min. The predicted concentration *versus* time curves represent the sampled arterial and venous sites as well as the idealized central compartment, the unmixed drug infusion artifact, and the arm compartment ketamine concentrations. With an infusion, more than 90% of the eventual steady-state arterial drug concentration for the unmixed, front-end component is reached by the end of the first minute. These initial, premixing arterial drug concentrations could have been observed had arterial sampling been as frequent as every 3 s, but with arterial sampling only several minutes apart in the current study, the earliest arterial drug concentrations have both central compartment (mixed) drug concentrations and unmixed drug concentrations during infusion.

After the infusion was stopped, arterial and central compartment ketamine concentrations become identical. During the infusion, arm veins and well-mixed central compartment ketamine concentrations are similar, and the predicted postinfusion venous concentrations differ from central compartment concentrations by the addition of a fraction of the arm compartment ketamine concentrations. This simulation demonstrates the feasibility of using pharmacokinetic modeling, coupled with an estimate of total pharmacokinetic flow, to convert venous drug concentrations to either arterial or central compartment drug concentrations and, conversely, to convert arterial drug concentrations to either venous or central compartment drug concentrations.

While the current analyses are purely pharmacokinetic, they have potential pharmacokinetic-pharmacodynamic modeling implications. It is widely assumed that arterial blood reflects the drug concentration seen at the effector organ(s). The results of the current analysis suggest that further mixing (*i.e.*, dilution) occurs at the small vessel (capillary) level during drug infusion. They further suggest that removal of this drug infusion artifact contaminating arterial blood samples could improve pharmacokinetic-pharmacodynamic modeling by, among other considerations,

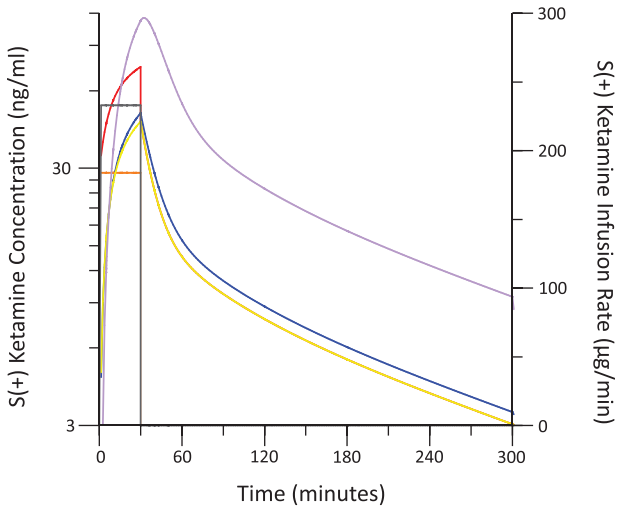

Fig. 6. Final model simulation of a 7 mg S(+)-ketamine dose infused at a constant rate during 30 min. The *solid red line* is arterial drug concentration, the *solid heavy blue line* is venous drug concentration, the *yellow line* is predicted concentration of the central compartment, the *lavender line* is drug concentration in the arm compartment, and the *orange line* is unmixed arterial drug concentration predicted by the ratio of infusion rate and ΣCl. Note that the *yellow* central compartment drug concentration *versus* time curve has a *green tinge* during the infusion (from confluence with the *blue* venous drug concentration curve) and an *orange tinge* postinfusion (from confluence with the *red* arterial drug concentration curve). The *right axis* and *dark gray line* represent the ketamine infusion rate.

reconciling the arterial drug concentration *versus* time profiles from different drug administration regimens, especially long *versus* short infusions, and the resultant divergence of pharmacokinetic-pharmacodynamic parameter estimates.

The current findings clearly demonstrate that a pharmacokinetic model based on arterial data will be quite different from one based on venous data even if those data are collected in the same subject at the same time (table 3), indicating that care should be taken when combining data from different studies. The results also suggest that the contribution of unmixed arterial drug concentrations will differ depending on the length of infusion (*e.g.*, bolus *vs.* long infusion) and perhaps constant rate *versus* target-controlled infusion. A varying infusion artifact will affect the arterial drug concentration *versus* time profile and, as a result, the model parameter estimates.

These results also match our previous findings in canines in which the distribution kinetics of S(+) and R(–) ketamine did not differ.[4] This was demonstrated first by the reduction in the Bayesian information criterion of a model with shared volumes of distribution and intercompartmental clearances from that of one with fully independent distribution parameters. Second, unlike the canine study in which only racemic ketamine was administered, in this study the entantiomers were administered on separate days, allowing statistical testing for interoccasion variability of S(+) *versus* R(–) distribution parameters. Even with this second layer of testing, no significant difference in distribution kinetics was found between the enantiomers.

Table 3. Results of the Three-compartment Models in which the Arterial and Venous Ketamine Concentration Data Were Fitted to Their Own Standard, Mammillary Models with the Distribution Kinetics of S(+) and R(–) Enantiomers Linked

	Typical Value Arterial	Typical Value Venous
V_C (l)	15.4	54.2
V_2 (l)	72.1	76.2
V_3 (l)	132	135
$Cle_{S(+)}$ (l/min)	1.52	1.49
$Cle_{R(-)}$ (l/min)	1.32	1.38
Cl_2 (l/min)	1.82	2.40
Cl_3 (l/min)	0.62	1.40
δ^2	0.21	0.21

The purpose of this table is to compare the typical parameter values. Note the large difference in central volume (V_C).

δ^2 = Intrasubject variability; Cl_2 and Cl_3 = intercompartmental clearance between the central compartment, V_C, and the rapidly and slowly equilibrating compartments, V_2 and V_3, respectively; Cl_e = elimination clearance for S(+) or R(–) ketamine, respectively.

Using equation 9 to correct the influence of different elimination clearances of the enantiomers on central volume demonstrated the feasibility of combining pharmacokinetic studies of the racemate with studies using the S(+) formulation into larger population studies, provided that potential interaction of entantiomers, when the racemate is administered, on their respective elimination clearances is examined and accounted for.[3]

In conclusion, population pharmacokinetic modeling demonstrated the superiority of a three-compartment model of ketamine that has the addition of a simple recirculatory compartment with clearance proportional to cardiac output to analyze ketamine concentrations in simultaneously obtained arterial and venous blood samples. This analysis suggests that arterial drug concentrations measured during drug infusion have an "infusion artifact" due to unmixed drug and that this concentration artifact is proportional to the ratio of drug infusion rate and cardiac output. The utility of this modeling approach for creating more generalizable models for target-controlled infusion and for analyzing pharmacokinetic-pharmacodynamic data will require further study.

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Competing Interests

The authors declare no competing interests.

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