Combined Recirculatory-Compartmental Population Pharmacokinetic Modeling of Arterial and Venous S(+) and R(-) Ketamine Concentration Data

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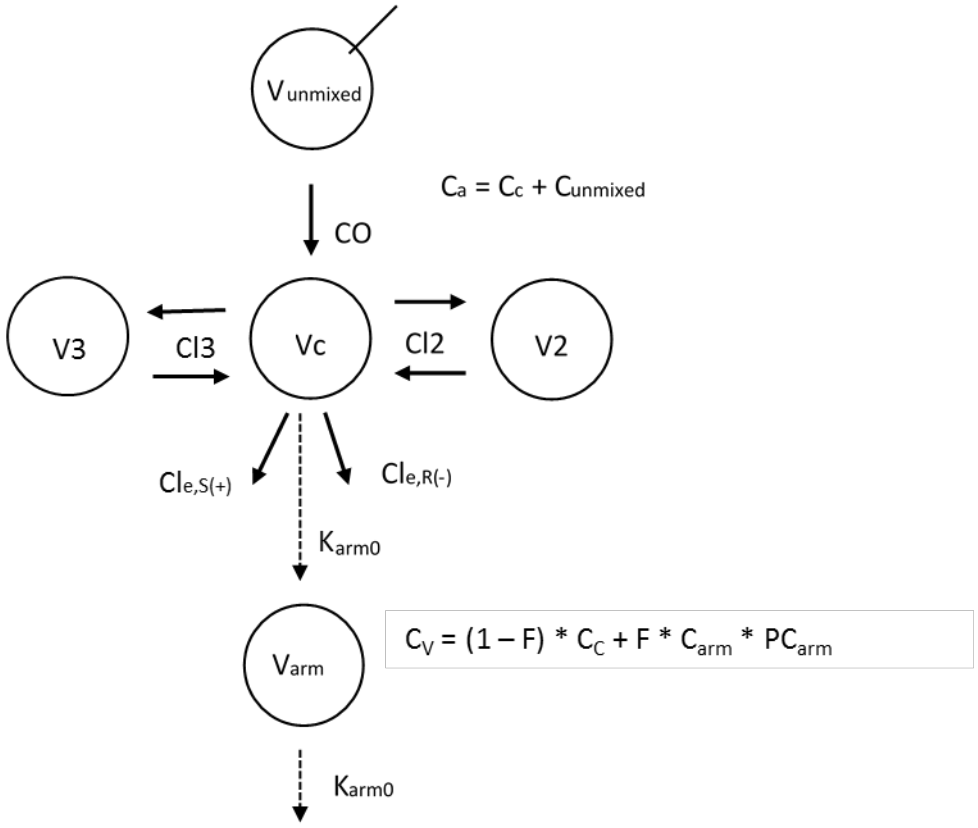
Introduction/Background: To date, pharmacokinetics (PK) of ketamine and other drugs infused by a constant rate infusion have been modeled without regard for recirculatory or mixing kinetics. We used a unique, ketamine dataset with simultaneous arterial and venous sampling, obtained during and after separate S(+) and R(-) ketamine infusions to develop a simplified recirculatory model of arterial and venous drug concentrations. We postulated that with A-V data, cardiac output and, thus, recirulatory kinetics could be directly estimated.

Methods: 7 mg of S(+) and R(-) ketamine were infused over 30 minutes on two occasions to 10 healthy male volunteers. Frequent, simultaneous arterial and forearm venous blood samples were obtained during and for up to 11 hours after the start of infusion. A multi-compartmental pharmacokinetic model with frontend mixing (cardiac output) and forearm kinetics, using a technique similar to an effect compartment model (see figure), was developed using population non-linear mixed effects analyses.

Results: A 3-compartment PK model with arterial mixing and arm venous compartments and with shared S(+)/R(-) distribution kinetics proved superior to standard independent compartmental modeling approaches. Cardiac output was estimated to be 6.52 $\pm$ 0.67 l/min (median $\pm$ SE) and S(+) and R(-) clearance were 1.33 $\pm$ 0.06 and 1.11 $\pm$ 0.05 l/min, respectively. The fraction of arm blood flow estimated to exchange with arm tissue was 0.05 $\pm$ 0.01; K_{arm0} (analogous to K_{e0}) was 0.11 $\pm$ 0.06 min^{-1} and tissue:plasma partition ratio was 3.90 $\pm$ 98.

Discussion: The current study shows that arterial drug concentrations measured during drug infusion have an 'infusion artifact' due to unmixed drug. Recirculatory kinetics demonstrate that this concentration artifact is equal to the ratio of infusion rate and cardiac output. This simplified frontend modeling approach could lead to more generalizable models for TCI and improved methods for analyzing PKPD data.
Figure 1.


Vunmixed
Ca = Cc + Cunmixed
CO
V3
Cl3
Vc
Cl2
V2
Cle,S(+)
Cle,R(-)
Karm0
Varm
CV = (1 – F) * CC + F * Carm * PCarm
Karm0