***Three-compartment model for ketamine concentration in brain tissue***

The three-compartment model is used to predict the concentration of ketamine in the brain. The model system is divided into three compartments: the first one (C1) encompasses the initial dilution volume, which is composed of the rapidly perfused tissues and organs. In considering the administered ketamine readily crosses the blood-brain-barrier and is rapidly distributed into the brain tissues ([White et al., 1982](#_ENREF_3)), we assumed that the ketamine concentration in the compartment-1 C1 is roughly proportional to the effective concentration needed for blocking the ketamine receptors such as NMDA receptor ([Schuttler et al., 1987](#_ENREF_2)). In addition, the elimination of ketamine is assumed as occurring directly and exclusively from C1. The second compartment (C2) involves the tissues and organs of the body which are less well perfused. Finally, an additional compartment (Ca) which denotes site of administration of ketamine is incorporated into the model.

At *t=t0*, a quantity D of ketamine is administered into the site of administration denoted as compartment-a (Ca). A fraction of F of the quantity D is then absorbed to the cerebral circulatory system (compartment-1, C1)from which it is both exchanged with compartment-2 (C2) and eliminated. This model assumes that all transfer processes follow first-order kinetics, and the brain is part of the C1.

 Assuming the absorption of ketamine is first-order process, the dynamic equation for the amount of ketamine *Xa*in Ca reads

$\frac{dX\_{a}}{dt}=-k\_{a}X\_{a}$ (S1.1)

where $k\_{a}$ denotes first-order absorption rate constant after the ip administration. We next consider variations of the amount of ketamine in the C1 with time, which are determined by the difference between the influx and efflux rates of the ketamine. Denoting the amount of ketamine in the C1 by *X1*, we thus write the equation for the dynamics of the *X1*:

 $\frac{ dX\_{1}}{dt}=k\_{a}X\_{a}-(k\_{12}+k\_{10}) X\_{1}+k\_{21}X\_{2}$*,* (S1.2)

where $k\_{12}$ and $k\_{21}$are the first-order transfer rate constant from C1 to C2 and C2 to C1, respectively. $k\_{10}$means the first-order elimination rate constant from C1. Note that in this model we assumed that ketamine elimination occurs only from the C1. The amount of ketamine in compartment-2 $X\_{2}$is given by

 $\frac{ dX\_{2}}{dt}=k\_{12}X\_{1}-k\_{21}X\_{2}$. (S1.3)

 Solving the equations with initial conditions $X\_{1}\left(t\_{0}\right)=X\_{2}\left(t\_{0}\right)=0$ and $X\_{a}\left(t\_{0}\right)=FD$ is straightforward to give the concentration of ketamine in each compartment at time *t* in the form:

 $c\_{a}\left(t\right)=\frac{FD}{V\_{a}}e^{-k\_{a}(t-t\_{0})}$*,* (S1.4)

$c\_{1}\left(t\right)=\frac{k\_{a}FD(k\_{21}-k\_{a})}{V\_{1 }\left(α-k\_{a}\right)(β- k\_{a})}e^{-k\_{a}(t-t\_{0})} + \frac{k\_{a}FD(k\_{21}-α)}{V\_{1 }\left(k\_{a}- α\right)(β- α)}e^{-α(t-t\_{0})}+ \frac{k\_{a}FD(k\_{21}-β)}{V\_{1 }\left(k\_{a}- β\right)(α - β)}e^{-β(t-t\_{0})}$*,*

(S1.5)

$c\_{2}\left(t\right)=\frac{k\_{12}k\_{a}FD}{V\_{2 }\left(α-k\_{a}\right)\left(β- k\_{a}\right)}e^{-k\_{a}\left(t-t\_{0}\right)} + \frac{k\_{12}k\_{a}FD}{V\_{2 }\left(k\_{a}- α\right)\left(β- α\right)}e^{-α\left(t-t\_{0}\right)}+ \frac{k\_{12}k\_{a}FD}{V\_{2 }\left(k\_{a}- β\right)\left(α – β\right)}e^{-β\left(t-t\_{0}\right)}$

(S1.6)

With $α=\left[k\_{10}+k\_{12}+k\_{21}+\sqrt{(k\_{10}+k\_{12}+k\_{21})^{2}-4k\_{21}k\_{10}}\right]/2$ and $β=\left[k\_{10}+k\_{12}+k\_{21}-\sqrt{(k\_{10}+k\_{12}+k\_{21})^{2}-4k\_{21}k\_{10}}\right]/2$, where $t\_{0}$ denotes the administration time. Here, we set $t\_{0}=0.$

With an assumption of linear relationship between $X\_{1}$ and behavioral effect of ketamine, it is assumed that $k\_{a}$ is inversely proportional to the interval between *t*LOM and *t*ADM with proportionality constant 1. The decay rate *α* is also assumed to be inversely proportional to the interval between *t*ROM and *t*LOM with an appropriate proportionality constant *c*, with which the mean value of *α*’s equals the first-order rate constant for distribution process calculated by conventional methods from the plasma concentration-time profile of ketamine in rodent ([Leung and Baillie, 1989](#_ENREF_1)). The other decay rate *β* and the rate constants $k\_{12}$, $k\_{21}$, and $k\_{10}$ are also determined from the time-concentration profile of ketamine ([Leung and Baillie, 1989](#_ENREF_1)). The resulting parameter values are displayed in Table S1.

**Reference**

Leung LY, Baillie TA (1989) Studies on the biotransformation of ketamine. II--Quantitative significance of the N-demethylation pathway in rats in vivo determined by a novel stable isotope technique. Biomedical & environmental mass spectrometry 18:401-404.

Schuttler J, Stanski DR, White PF, Trevor AJ, Horai Y, Verotta D, Sheiner LB (1987) Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers in man. Journal of pharmacokinetics and biopharmaceutics 15:241-253.

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