Electronic Supplementary Information

Calculation of partition coefficient plasma tissue

Drug concentration in a given tissue depends upon partition coefficient equilibriums, which describe the substance behavior in a tissue according to the pH it has, the physicochemical properties of the drug (pKa, K_{ow}), and the tissue composition in terms of water, neutral lipids, and phospholipids. There are several methods to estimate partition coefficients, the methods result in predictions with different accuracy depending on the tissue and the drug class[1,2]. In order to incorporate electrostatic interactions which might result in tissue binding, predictions for tissue distribution were calculated as described by Rodgers, Leahy and Rowland[3]. The equations employed for calculation of values for cocaine are shown below.

$$P_T = \frac{fu^p}{B:P} * Kup_t \quad \text{Eq.S1}$$

$$Kup = f_{EW} + \left(\frac{1+10^{pKa-pH_{IW}}}{1+10^{pKa-pH_p}} * f_{IW}\right) + \left(\frac{Ka*[AP^-]_T*10^{pKa-pH_{IW}}}{1+10^{pkA-pH_p}}\right) + \left(\frac{P*f_{NL}+((0.3P+0.7)*f_{NP})}{1+10^{pKa-pH_p}}\right) \quad \text{Eq.S2}$$

$$Ka_{BC} = \left(Kpu_{BC} - \left(\frac{1+10^{pKa-pH_{BC}}}{1+10^{pKa-pH_p}} * f_{IW,BC}\right) - \left(\frac{P*f_{NL,BC}+(0.3P+0.7)*f_{NP,BC}}{1+10^{pKa-pHp}}\right)\right) * \left(\frac{1+10^{pKa-pH_p}}{[AP^-]_{BC}*10^{pKa-pH_{BC}}}\right) \quad \text{Eq.S3}$$

$$Kpu_{BC} = \frac{B:P}{Ht*fu^p} - \frac{1-Ht}{Ht*fu^p} \quad \text{Eq.S4}$$

For equations S1 to S4 P_T= tissue partition coefficient; fu^p= unbound drug in plasma; B:P= blood-plasma ratio; Kup^t= unbound plasma: tissue partition coefficient f = tissue fractions of EW= extracellular water, IW= intracellular water, NL= neutral lipids, and NP= neutral phospholipids; pKa= ionization constant negative logarithm; P= octanol:water partition coefficient; pH_{IW}= intracellular water pH; pH_p= plasmatic pH; $[AP^-]_T$= tissue acidic phospholipids; Ka= ionization constant; Ka_{BC}= ionization constant in blood cells (BC); and Ht is hematocrit.

Since metabolite benzoylecgonine is a zwitterion, appropriate equations were employed to calculations according to Rodgers approach[4,5]

$$Kup = f_{EW} + \left(\frac{1+X}{1+Y} * f_{IW}\right) + \left(\frac{Ka*[AP^-]_T*X}{1+Y}\right) + \left(\frac{P*f_{NL}+((0.3P+0.7)*f_{NP})}{1+Y}\right) \quad \text{Eq.S5}$$

$$Ka_{BC} = \left(Kpu_{BC} - \left(\frac{1+Z}{1+Y} * f_{IW,BC}\right) - \left(\frac{P*f_{NL,BC}+(0.3P+0.7)*f_{NP,BC}}{1+Y}\right)\right) * \left(\frac{1+Y}{[AP^-]_{BC}*Z}\right) \quad \text{Eq.S6}$$

$$X = 10^{(pH_{IW}-pKa_{ACID})} + 10^{(pKa_{BASE}-pH_{IW})} \quad \text{Eq.S7}$$

$$Y = 10^{(pH_P-pKa_{ACID})} + 10^{(pKa_{BASE}-pH_P)} \quad \text{Eq.S8}$$

$$Z = 10^{(pH_{BC}-pKa_{ACID})} + 10^{(pKa_{BASE}-pH_{BC})} \quad \text{Eq.S9}$$

For equations 5 to 9 pKa_{ACID} = ionization constant negative logarithm of acid group; pKa_{BASIC}= ionization constant negative logarithm of basic group.

The tissue compositions and physiological blood data used for partition coefficients calculation are shown in tables 1 and 2. Cocaine physiological and pharmacological parameters used in the model are shown in table 3.

Tissue	Fractional Tissue Volume based on wet weight				Tissue Concentration of Acidic Phospholipids (mg/g)
	Neutral Lipid (f_{NL})	Neutral Phospholipid (f_{NP})	Extracellular Water (f_{EW})	Intracellular Water (f_{IW})	
Blood cells	0.0017	0.0029	---	0.603	0.5
Fat	0.853	0.0016	0.135	0.017	0.4
Bone	0.017	0.0017	0.1	0.346	0.67
Brain	0.039	0.0015	0.162	0.62	0.4
Intestine	0.038	0.0125	0.282	0.475	2.41
Heart	0.014	0.0111	0.32	0.456	2.25
Kidney	0.012	0.0242	0.273	0.483	5.03
Liver	0.014	0.024	0.161	0.573	4.56
Lung	0.022	0.0128	0.336	0.446	3.91
Muscle	0.01	0.0072	0.118	0.63	1.53
Skin	0.06	0.0044	0.382	0.291	1.32
Spleen	0.0077	0.0113	0.207	0.579	3.18

Table S1. Tissue Composition in rats as reported by Rodgers, Leahy and Rowland[3].

Parameter	Value	Reference
Plasmatic pH (pHp)	7.4	Waddell, 1969[6]
Intracellular water pH (pHIW)	7	Tehrani, 1982[7]
Blood cell pH (pHBC)	7.22	Kummerow, 2000[8]
Male rat hematocrit (Ht)	51.3	Arcila, 2010[9]

Table S2. Blood cell physiological data used in the model.

Parameter	Value
Partition coefficient logarithm from octanol:water of non-ionized molecule (Log P)	2.30[a]
Partition coefficient octanol:water (P)	199.53[a]

Plasmatic unbound fraction (fu_p)	0.68[b]
Blood - Plasma ratio (B:P)	1.01[b]
Ionization constant (pKa)	8.61[a]
Total rat clearance (CL_T)	0.0425 L/min [b]

Table S3. Cocaine physicochemical and pharmacological properties used in the model. Data obtained from: a) Wishart, 2010[10]; and b) Sukbuntherng, 1996[11].

Sensibility Analysis

Sensitivity analysis was conducted with Monte Carlo uncertainty analysis programmed in MATLAB (MATLAB R2017a). Model parameters were chosen from normal distributions for body weight and dose; and lognormal for everyone else considering a variability of 20% of the mean value (Confidence factor (Cf)=1.2, see Table 2 in the paper for details). The normalized sensitivity coefficient (NSC) values were determined by the following equation:

$$NSC = \frac{\Delta M}{m} * \frac{p}{\Delta p} \qquad \text{Eq.S10}$$

where m is the response variable (e.g., venous concentration), ΔM the change in response variable, p the value of the parameter, and Δp is the change in the parameter value. Variation in each parameter was considered according Table 2, and the NSCs were computed for a simulation of 32-mg/kg iv dose for a subject with body weight equal to 70 Kg. A small NCS value means that the variation in the parameter in question (i.e. Volume of heart (Vh) regarding maximum concentration peak in brain), does not result in an important change in the estimations by the PBPK model, it means that the estimation is not sensible to this parameter and therefore is not related importantly with the concentrations in that tissue. Resulting NCS are listed in Table S4

Table S4. Normalized sensitivity coefficient (NSC) values calculated at cocaine peak concentrations in brain (T=4.24) and in heart (T=3.41 min) from sensibility analysis by Monte Carlo from 1000 virtual subjects with body weight 70Kg and total dose of cocaine 32 mg. Values of NSC > 0.1 were considered relevant to simulation, these values are presented in bolt.

Parameter	Maximum brain peak concentration of cocaine (T=4.24 min)	Maximum heart peak concentration of cocaine (T=3.41 min)	Parameter	Maximum brain peak concentration of cocaine (T=4.24 min)	Maximum heart peak concentration of cocaine (T=3.41 min)
V_a	0.0187	0.0236	$V_{spleenv}$	0.0036	0.0036
V_{spleen}	0.0039	0.0035	V_{brainv}	0.0148	0.0035
V_{brain}	**0.3461**	0.0072	V_{hv}	0.0042	**0.2648**

V_h	0.0067	**0.3119**	V_{fv}	0.0037	0.0035
V_f	0.0039	0.0036	V_{Lv}	0.0048	0.0037
V_L	0.0336	0.0269	V_{bonev}	0.0041	0.0039
V_{bone}	0.008	0.0069	V_{intv}	0.0042	0.0041
V_{int}	0.009	0.0076	V_{lungv}	0.0038	0.0037
V_{lung}	0.0239	0.0226	V_{mv}	0.0083	0.0072
V_m	0.0142	0.0103	V_{sv}	0.0044	0.0047
V_s	0.0079	0.0075	V_{kv}	0.0038	0.0040
V_k	0.0121	0.0119			
V_v	0.0424	0.0606	CL_{COC}	**0.1329**	**0.1189**
Q_{spleen}	0.0059	0.0064	$K_{p:spleen}$	0.0037	0.0035
Q_{brain}	**0.3137**	0.0297	$K_{p:brain}$	**0.1062**	0.0077
Q_h	0.0055	**0.3088**	$K_{p:h}$	0.0047	**0.2143**
Q_f	0.0189	0.0171	$K_{p:f}$	0.0039	0.0036
Q_L	0.0712	0.0659	$K_{p:L}$	0.0128	0.0080
Q_{ha}	0.0168	0.0133	$K_{p:bone}$	0.0038	0.0035
Q_{bone}	0.0054	0.0058	$K_{p:int}$	0.0040	0.0036
Q_{int}	0.0361	0.0372	$K_{p:lung}$	0.0054	0.0045
Q_m	0.0412	0.0419	$K_{p:m}$	0.0038	0.0035
Q_s	0.0084	0.0067	$K_{p:s}$	0.0037	0.0035
Q_k	0.0369	0.0304	$K_{p:k}$	0.0044	0.0039
PS_f	0.004	0.0038			
PS_{skin}	0.0061	0.0051			
PS_{bone}	0.0064	0.0053			
PS_m	0.007	0.0049			
PS_h	0.0039	0.0231			
PS_{int}	0.0064	0.0055			
PS_{spleen}	0.0040	0.0038			
PS_L	0.0197	0.018			
PS_k	0.0084	0.0081			
PS_{brain}	0.0049	0.0037			
PS_{lung}	0.0169	0.0175			

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