



In vivo blood-brain barrier transport of oxycodone in the rat – active influx and implications for PK/PD

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Aim: To investigate the *in vivo* blood-brain barrier (BBB) transport of oxycodone in rats.

Introduction: Brain distribution can be described with respect to the rate and extent of equilibration of a drug molecule across the BBB (1). The rate of equilibrium can be expressed as clearances into and out of the brain, CL_{in} and CL_{out} , respectively. The extent of equilibration across the BBB can be expressed as the ratio of the steady-state concentration of unbound drug in brain over unbound drug in blood, $K_{p,uu}$ (2). If $K_{p,uu}$ is below unity, a likely explanation is active efflux transport, metabolism at the BBB or substantial influence of bulk flow on drug brain elimination. A $K_{p,uu}$ above unity is an indication that active influx processes, such as influx transport is involved in the BBB transport.

Methods: Microdialysis probes were inserted into the striatum and vena jugularis. Ten animals were given a bolus dose followed by a 120 minute constant rate infusion to study the steady-state concepts of oxycodone BBB equilibration. Another ten animals were given a 60 minute constant rate infusion to study the rate of equilibration across the BBB. Oxycodone-D3 was used as a calibrator for the microdialysis experiments. A population pharmacokinetic model was used to simultaneously fit all the data using NONMEM.

Results: A two-compartment model which allowed for a delay between the venous and arterial compartments best described the pharmacokinetics for oxycodone in blood and plasma, while a one-compartment model was sufficient to describe the pharmacokinetics in the brain (Fig. 1). The BBB transport of oxycodone was parameterized as CL_{in} and $K_{p,uu}$. CL_{in} across the BBB was estimated to 1910 $\mu\text{L}/\text{min}\cdot\text{g}$ brain. $K_{p,uu}$ was estimated to 3.0, meaning that the unbound concentration of oxycodone in brain was 3 times higher than in blood, which is an indication of active influx of oxycodone at the BBB.

	Original Data Set		Bootstrap Resampling	
	Estimate	RSE ^a (%)	Mean	RSE ^a (%)
CL (mL/min)	37.4	3.4	37.6	3.1
Vc (mL)	1010	5	1016	4.8
Q (mL/min)	4.37	19	4.40	19
V _{per} (mL)	230	13	234	13
Q _{AV} (mL/min)	45.1	7.9	45.2	8.1
f _u (%)	74.3	7.1	74.3	6.7
REC _{blood} (%)	65.8	2.3	65.8	2.4
REC _{brain} (%)	16.4	6	16.5	6.1
CL _{in} (mL/min)	1.91	20	1.95	20
K _{p,uu}	3.03	3.8	3.04	3.7
Inter animal variability				
ω_{cl}	0.14	33	0.14	34
ω_{vc}	0.16	36	0.16	39
ω_{fu}	0.28	51	0.26	52
$\omega_{REC_{blood}}$	0.10	28	0.097	30
$\omega_{REC_{brain}}$	0.22	31	0.21	32
Residual variability				
$\sigma_{prop,plasma}^b$ (%)	0.195	9.3	0.189	9.6
$\sigma_{prop,blood}^b$ (%)	0.171	8.1	0.169	8.5
$\sigma_{prop,brain}^b$ (%)	0.152	18	0.143	20
$\sigma_{add,brain}^c$ (mg/mL)	0.226	42	0.224	43
$\sigma_{add,REC_{blood}}^c$ (mg/mL)	2.44	12	2.43	11
$\sigma_{add,REC_{brain}}^c$ (mg/mL)	2.07	12	2.03	12

Table 1. Unbound parameter estimates of the final population pharmacokinetic model for oxycodone and the stability of the parameters using bootstrap resampling validation.

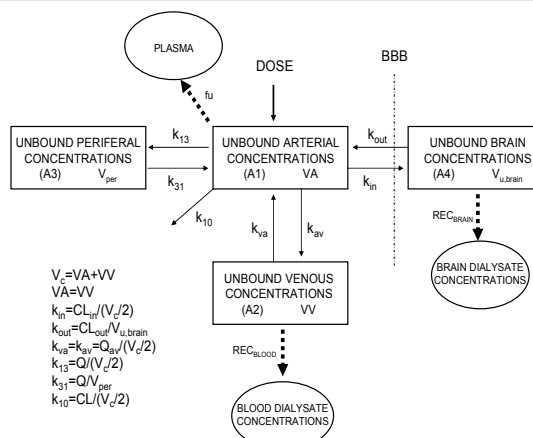


Fig 1. A schematic view of the model describing the systemic pharmacokinetics and the blood-brain barrier transport of oxycodone. The circles represent the observed data. Dotted arrows represent the transformations made from the observed data to obtain the unbound concentrations in brain and blood. Thin arrows represent mass transport. The conversions from rate constants to the estimated unbound parameters are shown in the legend.

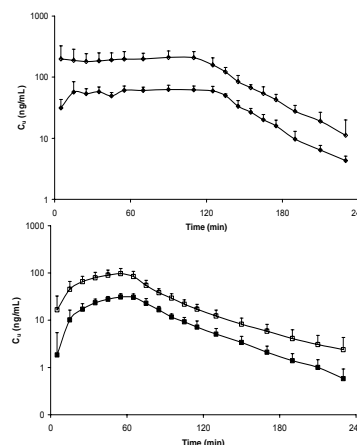


Fig. 2. Observed concentration-time profiles of unbound oxycodone concentrations (mean \pm SD) a) in brain (\circ) and blood (\bullet) of rats receiving a bolus dose followed by a 120 min constant rate infusion of oxycodone, and b) in brain (\square) and blood (\blacksquare) of rats receiving a 60 minute constant rate infusion of oxycodone.

Discussion: This is the first evidence of an opioid having an unbound steady-state concentration in brain that is higher than in blood. Other opioids have much lower ratios, the $K_{p,uu}$ for morphine was for example 0.29 (3). The observation of a $K_{p,uu}$ for oxycodone greater than unity might explain the equi-analgesic potency of oxycodone and morphine *in vivo*, in spite of the much weaker μ -receptor affinity of oxycodone compared to morphine.

Conclusion: The unbound steady-state concentration in brain was 3 times higher than in blood, which is an indication of active influx at the BBB.

References:

1. M. Hammarlund-Udenaes. *Adv Drug Deliv Rev* 45: 283-94. (2000).
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3. K. Tunblad, E. N. Jonsson, and M. Hammarlund-Udenaes. *Pharm Res* 20: 618-23 (2003).