



Oxymorphone pharmacokinetic-pharmacodynamic relationship and blood-brain barrier transport studied with microdialysis

Muhammad Waqas Sadiq¹, Emma Boström², Ron Keizer¹, Sven Björkman¹, Margareta Hammarlund-Udenaes¹
¹Dept of Pharmaceutical Biosciences, Uppsala University, Sweden. ²AstraZeneca R&D Södertälje, Sweden.

Objective

- To characterize the BBB transport and pharmacokinetic and pharmacodynamic (PKPD) relationship of oxymorphone in rats using population modeling.

Methods

Transport of oxymorphone across the BBB was studied with microdialysis (MD) in male Sprague-Dawley rats. Samples from microdialysis blood and brain probes were analyzed with LC-MS/MS. The analgesic effect of oxymorphone was studied by measuring the tail flick latency. The study consisted of a PKPD experiment with combined microdialysis and antinociceptive effect measurements (Group 1, $n = 8$) as well as a separate antinociceptive effect experiment (Group 2, $n = 9$). In Group 2, the dose of oxymorphone administered was 10 times lower than in Group 1. Non-linear mixed effects modeling was used to analyze the PK data from plasma, MD brain and blood samples and the PD data of tail flick latency, using NONMEM, and Pirana as the modeling environment. Censored observations in the PD data from Group 1 were treated with the 'M3 method' adapted to handle data above the upper limit of quantification (15 seconds) in the PKPD model in order to fully utilize the PD information. Model selection and evaluation was performed using likelihood ratio tests and visual predictive checks.

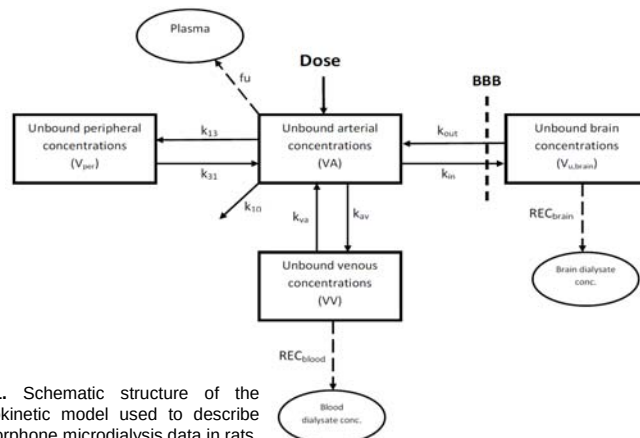


Figure 1. Schematic structure of the pharmacokinetic model used to describe the oxymorphone microdialysis data in rats.

Results

- Oxymorphone had higher unbound concentration in brain than in blood with a ratio of unbound drug in brain interstitial fluid to unbound in blood ($K_{p,uu}$) of 1.87 (10%), indicating the presence of active uptake transport of oxymorphone (Fig. 2).

- The uptake clearance (CL_{in}) into the brain for oxymorphone was 72.4 $\mu\text{L}/\text{min}/\text{g-brain}$ and the efflux clearance (CL_{out}) was 38.7 $\mu\text{L}/\text{min}/\text{g-brain}$.

- The integrated PK model with an Emax effect model best described the oxymorphone BBB transport and PKPD relationship. All parameters were estimated with high precision ($\text{RSE} < 15\%$), except for EC_{50} and E_{max} . The EC_{50} (unbound brain concentrations) of oxymorphone was estimated to 62.6 (82%) ng/mL , corresponding to an unbound plasma EC_{50} of 33.5 ng/mL .

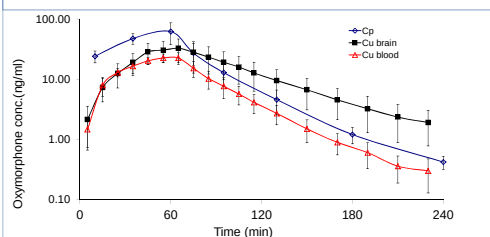


Figure 2. Concentration profiles over time for oxymorphone in plasma (blue), unbound oxymorphone in brain (black) and unbound oxymorphone in blood (red) (Group 1).

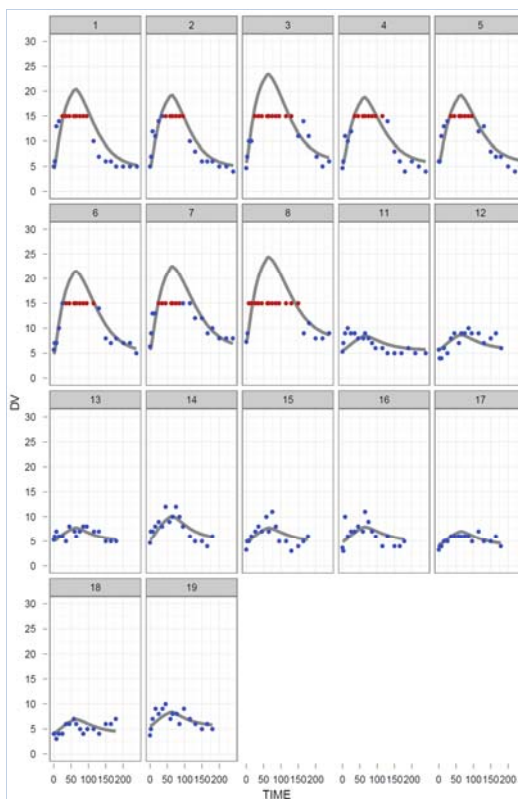


Figure 3. Tail-flick latency profiles for Group 1 (animals 1-8) and Group 2 (animals 11-19). Effect profiles were also estimated for the censored data for all animals in Group 1. Each red circle indicates a censored observation.

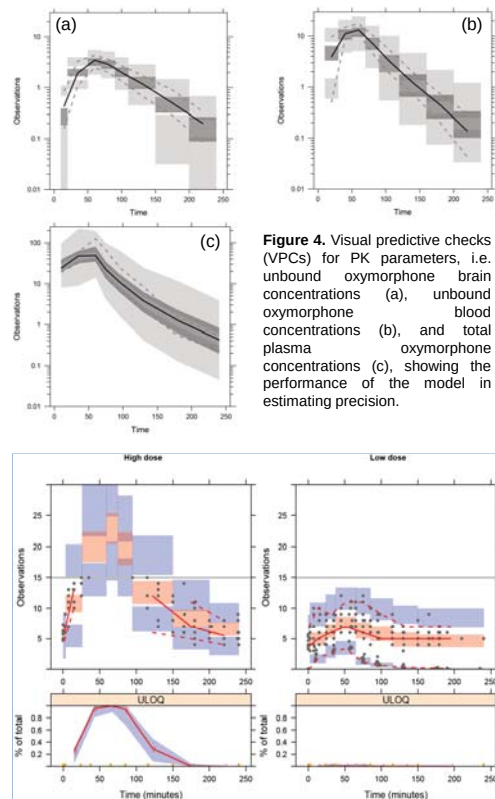


Figure 4. Visual predictive checks (VPCs) for PK parameters, i.e. unbound oxymorphone brain concentrations (a), unbound oxymorphone blood concentrations (b), and total plasma oxymorphone concentrations (c), showing the performance of the model in estimating precision.

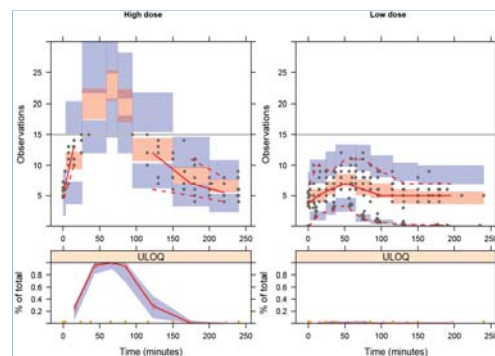


Figure 5. Visual predictive checks (VPCs) for the PD measurements for Group 1 (high dose) and Group 2 (low dose). The lower panel represents the percentage of censored data as a proportion of total observations.

Conclusions

- Oxymorphone has an active uptake transport at the BBB in rats similar to oxycodone, but with a moderate uptake clearance into the brain.
- The effect profile was successfully described using the modified M3 method for censored observations, demonstrating that modeling of tail-flick data is advantageous, given the experimental limitations of the method.
- Considering the results obtained in this study, it can be concluded that the contribution of oxymorphone to the analgesic effect of oxycodone would be minor.