Oxymorphone Active Uptake at the Blood–Brain Barrier and Population Modeling of its Pharmacokinetic–Pharmacodynamic Relationship

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ABSTRACT: The aim of this study was to characterize the blood–brain barrier (BBB) transport and pharmacokinetics–pharmacodynamics (PKPD) relationship of oxymorphone and to further elucidate its possible contribution to oxycodone analgesia. The BBB transport of oxymorphone was studied using microdialysis in male Sprague–Dawley rats. Samples from microdialysis blood and brain probes, brain tissue, and plasma were analyzed by liquid chromatography with tandem mass spectrometry. The effect was measured as tail-flick latency. The study consisted of a PKPD experiment with combined microdialysis and antinociceptive measurements ($n = 8$), and another antinociceptive effect experiment ($n = 9$) using a 10 times lower dose. The combined data were analyzed with an integrated PKPD model in nonlinear mixed effect modeling utilizing a specific method (M3) for handling missing PD observations. The concentration of unbound oxymorphone was higher in brain than in blood, with a ratio of 1.9 (RSE, 9.7%), indicating active uptake at the BBB. The integrated PKPD model described the oxymorphone BBB transport and PKPD relationship successfully, with an EC_{50} in the brain of 63 ng/mL, and the M3 method was able to address the issue of censored observations. Oxymorphone has active uptake transport at the BBB in rats, with moderate uptake clearance to the brain. Its contribution to analgesia after oxycodone administration is not significant. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3320–3331, 2013

Keywords: Blood brain barrier; active transport; pharmacokinetic/pharmacodynamic models; Microdialysis; HPLC; analgesia; NONMEM; E_{max} model; censored observations

INTRODUCTION

Oxymorphone is a semi-synthetic opioid analgesic used to treat postoperative and cancer-related pain. It is also formed as a metabolite of oxycodone by 3-O-demethylation, catalyzed by cytochrome P450 (CYP) 2D6 in the human liver.[1] Oxymorphone produces most of its antinociceptive effects through μ and δ opioid receptors.[2] Its affinity for the μ-receptor is at least four times higher than that of morphine[3–5] and at least 10–45 times higher than that of oxycodone.[4–6] Oxymorphone is approximately nine times more potent than morphine based on dose, when comparing the duration and intensity of analgesia in humans.[7] It produces equivalent analgesia to oxycodone at half the oral dose.[8] On the basis of these findings, it has been speculated that oxymorphone might contribute to the overall analgesic effect of oxycodone. However, inhibition of the metabolism of oxycodone by quinine in rats had no effect on the level of analgesia,[9] and pharmacodynamic (PD) studies on oxycodone in humans have failed to find significant contributions of oxymorphone to the overall opioid effects.[10–12] There are several possible explanations for this. It is

Abbreviations used: CNS, central nervous system; BBB, blood–brain barrier; PKPD, Pharmacokinetics-pharmacodynamics; LC–MS/MS, liquid chromatography with tandem mass spectrometry; NONMEM, nonlinear mixed effect modeling; RSE, relative standard error; LOQ, limit of quantification; VPC, visual predictive checks; OFV, objective function value.

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therefore important to quantify the blood-to-brain distribution and PD of oxymorphone to understand its probable lack of contribution to oxycodone analgesia.

To reach the opioid receptors within the central nervous system (CNS), the drug must penetrate through the protective blood–brain barrier (BBB) of vascular endothelial cells with enforced tight junctions and efflux transporters. When the mean total brain-to-plasma concentration ratios ($K_{p,brain}$) of oxycodone and oxymorphone were measured in rats,[12] the oxymorphone $K_{p,brain}$ was 0.23, comparable to that of morphine but one-tenth of that of oxycodone. This lower $K_{p,brain}$ of oxymorphone was suggested to play an important role in limiting its CNS effects. However, a low $K_{p,brain}$ for total drug concentrations does not necessarily mean poor transport or predominating efflux for that drug across the BBB[13]; it could be the result of high protein binding in plasma combined with relatively low nonspecific binding to brain tissue. Thus, to understand the BBB transport of a drug, it is of prime importance to measure the concentrations of unbound drug in the brain. This can be accomplished with microdialysis.

Because of the presence of the efflux transporters, the concentration of unbound morphine is much lower in the brain than in the blood in rats and humans.[14,15] For oxycodone and diphenhydramine in rats,[16,17] and morphine in sheep,[18] the unbound concentrations are however higher in the brain, indicating active uptake transport for these cationic drugs. Oxycodone was reported to have an unbound brain to plasma concentration ratio ($K_{p,uu}$) of 3 in rats with a brain uptake clearance of 1910 μL/min.[16] Oxymorphone is very similar to its parent drug oxycodone, whereas oxidative removal of the 3-methyl group makes it to be structurally closer to morphine (Fig. 1). The question is thus: will oxymorphone show an oxycodone-like net influx into, or a morphine-like net efflux from the CNS?

The aim of this study was therefore to characterize the BBB transport and pharmacokinetic–pharmacodynamic (PKPD) relationship of oxymorphone in rats based on its unbound concentrations in blood and brain. The dose level necessary to achieve measurable levels of oxymorphone in brain microdialysate produced analgesic effects above the 15 s cutoff of the tail-flick PD measurement [limit of quantitation (LOQ)]. The M3 method[19] was implemented for population-based PKPD modeling of antinociceptive effect measurements above the LOQ to utilize all data for understanding the PKPD relationship of oxymorphone.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats were obtained from Scanbur BK, Sollentuna, Sweden. The animals were acclimatized for 1 week before the experiment and were group housed at 22°C in a 12 h day–night cycle with free access to food and water. The study protocol was approved by the Ethics Committee for Animal Research, Tierps District Court, Tierp, Sweden (C176/4 and C177/4). The rats weighed 240–310 g on the day of surgery.

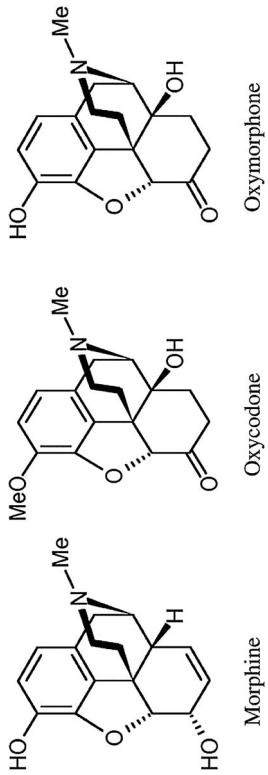

Figure 1. Chemical structures of morphine, oxycodone and oxymorphone.

Chemicals

All chemicals were of analytical grade. All solvents were of high-performance liquid chromatography grade. Acetonitrile, ammonium acetate, and perchloric acid were obtained from Merk (Darmstadt, Germany). Oxymorphone and oxymorphone-D_3 dissolved in methanol were purchased from Cerilliant (Round Rock, Texas). The perfusate for the microdialysis probes was a Ringer solution prepared by dissolving NaCl 147 mmol/L, KCl 2.7 mmol/L, $CaCl_2$ 1.2 mmol/L, and $MgCl_2$ 0.85 mmol/L in MilliQ water (Millipore, Bedford, Massachusetts). NaCl, KCl, $CaCl_2 \times 2H_2O$, and $MgCl_2 \times 6H_2O$ were all obtained from Merck. The Ringer solution was filtered through a 0.2 μm Supor® Membrane (Pall Gelman Laboratory, Ann Arbor, Michigan) and frozen until use. Deionized water was purified further with a Milli-Q Academic system (Millipore).