Nonlinear blood-brain barrier transport and dosing strategies influence receptor occupancy ratios of morphine and its metabolites in pain matrix.

Divakar Budda[1], Berfin Gülave[1], Johan G. C. van Hasselt[1], and Elizabeth De Lange[1]

[1] Leiden Academic Center for Drug Research

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Abstract

Background & purpose Morphine is important for treatment of acute and chronic pain. However, there is high interpatient variability and often inadequate pain relief and adverse effects. To better understand variability in the dose effect relationships of morphine, we investigated the impact of its nonlinear blood-brain-barrier (BBB) transport on mu-opioid receptor (μ-OR) occupancy in different CNS locations, in conjunction with its main metabolites that bind to the same receptor. Methods CNS exposure profiles for morphine, M3G and M6G for clinically relevant dosing regimens based on intravenous, oral immediate- and extended-release formulations were generated using a CNS PBPK model which incorporated nonlinear BBB transport of morphine. The simulated CNS exposure profiles were then used to derive corresponding μ-OR occupancies at multiple CNS pain matrix locations. Results The simulated CNS exposure profiles for morphine, M3G and M6G, associated with nonlinear BBB transport of morphine resulted in varying μ-OR occupancies between the different dose regimens, formulations, and CNS locations. We find that at lower doses, the μ-OR occupancy of morphine was relatively higher than at higher doses of morphine, due to the relative contribution of M3G and M6G. At such higher doses, M6G showed higher occupancy than morphine, whereas M3G occupancy was low throughout the dose ranges. Conclusion and implications Nonlinear BBB transport of morphine influences the μ-OR occupancy ratios of morphine and its metabolites, depending on dose and route of administration, and CNS location. This may impact the clinical effects of morphine treatment for pain relief.

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