Morphine is a Substract of OATP Uptake Transporters in Vitro

Background: Opioids like morphine are highly potent analgesics but exert a significant interindividual variability in disposition and clinical effects. This results in a considerable risk of both, persisting pain and adverse drug reactions due to genetic variability or drug interactions. Known determinants of morphine pharmacokinetics (i.e. UGT2B7, P-gp, MRP3, OCT1) can only partially explain its effect variability. Furthermore, mechanisms of intestinal and brain uptake of morphine are still unknown. Uptake transporters of the organic anion transporting peptide family (OATPs) mediate the uptake of a broad spectrum of drugs across biological barriers, including the intestine and the blood-brain barrier. Thus, OATPs could possibly be involved in morphine pharmacokinetics and variability. However, evidence for morphine uptake by OATPs is lacking. Therefore, this study investigated the cellular uptake of morphine by OATPs in a cell model.

Methods: Human embryonic kidney cells stably over-expressing OATP1A2, OATP1B1, OATP1B3 or OATP2B1 were incubated with radiolabeled morphine. Cellular morphine uptake was measured by liquid scintillation counting after cell lysis. Enhancement of morphine uptake by OATPs vs. control cells was tested in a preliminary screening. Detailed characterization of morphine transport consisted of time-dependent (10 s – 30 min; 10 nM morphine) and concentration-dependent (0.3 nM – 1 mM morphine; 1 min) uptake assays. Furthermore, inhibition of morphine uptake by the established OATP inhibitors naringin and rifampicin (0 – 1 mM inhibitor; 500 µM morphine) was investigated.

Results: Morphine was a substrate of OATP1A2, OATP1B1 and OATP2B1 but not of OATP1B3. Morphine uptake via OATP1A2, OATP1B1 and OATP2B1 was time- and concentration-dependent, followed typical Michaelis-Menten kinetics (K_m 0.76 – 1.02 mM; V_{max} 5.6 – 6.7 nmol/mg×min), and was inhibitable by naringin and rifampicin (IC_{50} 0.85 – 3.0 µM, maximum inhibition 69 – 93%).

Conclusions: OATPs might play a role in morphine pharmacokinetics and variability. However, further investigations are necessary to establish the clinical relevance of OATPs and their genetic variants in morphine treatments.