**Morphine and Hydromorphone Interact Differently with Uptake Transporters of the OATP Family**

Anett Engel, PhD, Universitätsmedizin Greifswald, Tabea Sieling, Julia Kolbow, Annette Wegner, MEng, Markus Keiser, DVM, Werner Siegmund, MD, Konrad Meissner, MD, Universitätsmedizin Greifswald

**Background/Introduction:** Transmembrane transport processes mediated by ABC (ATP-binding cassette)-type proteins play an important role in absorption, distribution and elimination of different drugs. Several opioids like loperamide, morphine, and methadone are known substrates of the efflux transporter P-glycoprotein (ABCB1, MDR1), which limits access of its substrates to the brain at the apical side of endothelial cells of the blood-brain barrier, restricts absorption from the gut at the apical side of enterocytes and supports active secretion at the apical side of hepatocytes and proximal tubule cells in the kidney. In contrast, OATP (organic anion transporting polypeptide)-type transmembrane transport proteins facilitate the uptake of drugs into the brain at the apical side of endothelial cells (OATP1A2, OATP2B1), into the liver at the basolateral side of hepatocytes (OATP1B1, OATP1B3, OATP2B1) for subsequent metabolism, and enable resorption from the gut at the apical side of enterocytes (OATP1A2, OATP2B1).1;2 However, the interaction of opioids with such transporters has not been sufficiently studied so far. Therefore, the present study investigated the influence of morphine and hydromorphone on multispecific uptake transporters of the OATP family *in-vitro*.

**Methods:** HEK 293 cells were stably transfected with OATP1A2, OATP1B1, OATP1B3, OATP2B1 or the empty vector as control. Inhibitory effects of increasing opioid concentrations were studied in competition assays (n=9) using established, radiolabelled reference substrates. Intracellular accumulation of estrone-3-sulfate (OATP1A2) and bromosulfophthalein (OATP1B1, OATP1B3, OATP2B1) was measured by liquid scintillation counting after cell lysis. Furthermore, cellular uptake of radiolabelled morphine into OATP2B1 cells was assessed (n=9).

**Results:** Both opioids interacted with all investigated OATPs with exception of morphine and OATP2B1 (table 1). Generally, hydromorphone exhibited a higher affinity to OATPs than morphine. Both opioids completely inhibited OATP1A2 but only slightly influenced OATP1B1 and OATP1B3. Major differences were observed for OATP2B1: while hydromorphone was a potent inhibitor, morphine was neither inhibitor nor substrate of this transporter.

**Conclusion:** Morphine and hydromorphone were shown to interact with various OATPs. In general, hydromorphone exhibited a larger spectrum and inhibitory potential among OATPs than morphine *in-vitro*. These findings suggest that OATPs might play a distinctive role in pharmacokinetics and thus drug effect variability of these two clinically important opioids. Further investigations are necessary to elucidate how morphine and hydromorphone effects vary due to drug uptake transport *in-vivo*.

**Table 1:** Inhibition of uptake transporters of the organic anion transporting polypeptide family by morphine and hydromorphone.

|  |  |  |
| --- | --- | --- |
|  | Morphine | Hydromorphone |
| Transporter | IC50 (µM) | MIE (%) | IC50 (µM) | MIE (%) |
| OATP1A2 | 44 | 100 | 7.5 | 100 |
| OATP1B1 | 31.4 | 22.5 | 0.28 | 32 |
| OATP1B3 | 8.0 | 62 | 3.8 | 38 |
| OATP2B1 | --- | no effect | 5.9 | 78 |

IC50 – half maximal inhibitory concentration; MIE – maximal inhibitory effect

**References:**

 1. Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin A, Evers R, Fischer V, Hillgren KM, Hoffmaster KA, Ishikawa T, Keppler D, Kim RB, Lee CA, Niemi M, Polli JW, Sugiyama Y, Swaan PW, Ware JA, Wright SH, Yee SW, Zamek-Gliszczynski MJ, Zhang L: Membrane transporters in drug development. Nat.Rev.Drug Discov. 2010; 9: 215-36

 2. Hagenbuch B, Gui C: Xenobiotic transporters of the human organic anion transporting polypeptides (OATP) family. Xenobiotica 2008; 38: 778-801