

University of Maryland Baltimore Graduate School

Announcement of Doctoral Dissertation Defense*

Candidate: Hazem Emad Eldin Hassan Abdel Hamid

Date, Time, and Place: 09/28/2007, 9:00 a.m., HSFII room 600

Dissertation Title: Evaluation of The Influence of Chronic Opioid Administration on Gene Expression, and Characterization of The Role of Efflux Transporters on The Pharmacokinetics, Pharmacodynamics and Drug-Drug Interactions of Opioids for Effective Management of Pain

Dissertation Abstract**:

Being P-gp substrates is one of the major shortcomings of the currently used opioids. P-gp was demonstrated to extrude opioids out of the CNS and the systemic circulation leading to minimized opioid-opioid receptors interaction and subtherapeutic plasma levels, respectively. In addition, P-gp affected the cellular uptake, tissue distribution, oral absorption and systemic elimination of opioids that are P-gp substrates. Many opioids (e.g., oxycodone, buprenorphine) were used for decades for management of pain, however, information regarding their interactions with P-gp is insufficient or lacking. P-gp is upregulated in brain tissues of morphine (P-gp substrate) tolerant rats but whether P-gp or any other transporters are regulated upon chronic administration of any other opioid (e.g., oxycodone) is yet to be elucidated. Moreover, opioids are usually concomitantly administered with many therapeutic agents that are substrates or inhibitors for transporters or metabolizing enzymes. Evaluation of the level of expression of transporters and metabolizing enzymes upon chronic opioid administration is of extreme importance since they can affect the PK/PD of opioids and mediate drug-drug interactions. **Objectives:** 1) to evaluate the P-gp affinity status of the currently available opioids to identify candidates that lack P-gp interactions to help improve pain management, 2) to identify transporters and metabolizing enzymes that are regulated upon chronic opioid (oxycodone) administration to help predict and overcome drug-drug interactions. **Methods:** Systematic *in vitro* (P-gp ATPase and Caco-2 transport assays) and *in vivo* (biodistribution and antinociceptive monitoring in P-gp knockout mice) approaches were used to elucidate the P-gp affinity status of 29 opioids. In addition, we used microarray, gene mapping, Q-PCR and Western blot analysis to determine the level of expression of transporters and metabolizing enzymes in brain and liver tissues of oxycodone treated rats. Finally, transporters mediated drug-drug interactions between oxycodone and chemotherapeutic agents [e.g., paclitaxel (P-gp substrate), and mitoxantrone (Bcrp substrate)] were evaluated. **Results:** Out of 29 tested opioids, 17 opioids were P-gp substrates (e.g., oxycodone) while 12 opioids exhibited no interaction with P-gp (e.g., 6-desoxymorphine). Oxycodone administration regulated the expression of many genes including: nuclear receptors (Pxr and Car), ~40 transporters (e.g., P-gp and Bcrp), and 20 metabolizing enzymes (e.g., Cyp3a1, Sult1a1). In addition, in oxycodone treated rats, P-gp induction restricted paclitaxel distribution to the liver, kidney and brain, while Bcrp induction hindered the brain uptake of mitoxantrone. **Conclusion:** P-gp affected the PK/PD of many opioids that are P-gp substrates (e.g., oxycodone, methadone, and many morphine and meperidine analogs). Oxycodone regulated the expression of P-gp and many other transporters and metabolizing enzymes which could be the locus of drug-drug interactions when substrates for these transporters/metabolizing enzymes are co-administered with oxycodone. On the other hand, many opioids that lack interactions with P-gp were identified. For these opioids, concerns regarding the influence of P-gp on their PK/PD will not be expected. These opioids are expected to have better BBB permeability, better antinociceptive activity, delayed development of tolerance, minimal P-gp-mediated drug-drug interactions and would be better candidates for management of pain.

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