

Human BioMolecular



Research Institute

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“N-Oxygenation of Oxycodone and Retro-Reduction of Oxycodone N-Oxide”.

New metabolite of oxycodone quantified in humans, featured in *Drug Metabolism and Disposition*.

San Diego, Calif., November 15, 2019 - Researchers at the Human BioMolecular Research Institute and Pain Therapeutics, Inc., (now Cassava Sciences, Inc.) reported that a new metabolite of oxycodone was quantified in rat and humans. Publishing November 15, 2019, in *Drug Metabolism and Disposition*, the team describes how they identified and characterized a new metabolite of oxycodone, oxycodone-N-oxide. Oxycodone-N-oxide is also retro-reduced by reductases to afford oxycodone in newly described metabolic pathways.

Oxycodone is a potent medication used as an analgesic and antitussive. Oxycodone is also used for severe pain associated with arthritis, disc disease and cancer. The potential beneficial properties of oxycodone for pain is confounded by its incidence of addiction liability. Oxycodone and its metabolite oxymorphone are potent mu opioid receptor agonists but are extensively metabolized. The team identified and characterized two new metabolic pathways for oxycodone.

“We need to develop effective new medications for pain, and part of that process is to understand the metabolism and biodistribution of existing pain drugs” said John Cashman, Ph.D., President of Human BioMolecular Research Institute and co-author of the study. “It may be that a more thorough understanding of the metabolism of a widely used drug such as oxycodone could lead to new medications development.”

Two new metabolic pathways involving oxycodone

A team of scientists at Pain Therapeutics, Inc., and the Human BioMolecular Research Institute, led by John Cashman, Ph.D., using modern bioanalytical and biochemical procedures, identified oxycodone N-oxide as a metabolite of oxycodone in vitro and in vivo. Oxycodone N-oxide was retro-reduced to oxycodone in a robust process involving at least 3-4 reductase systems. Retro-reduction of oxycodone N-oxide contributed to a meaningful part of the overall metabolism.

“Oxycodone N-oxide appears to have significant properties to provide a potential reservoir of oxycodone and oxycodone metabolites for analgesia,” explained Jiongjia Cheng, Ph.D., a leading researcher in Cashman’s lab but not a co-author of the paper.

Oxycodone N-oxide Formation and Retro-Reduction

Developing new medications for pain and other conditions is important. Currently, oxycodone is an important analgesic but has been associated with significant addiction liability. For pain medication drug development the difficult part is: 1) identifying a potent compound with appropriate onset of action and 2) designing a compound with low abuse and addiction liability.

Human liver microsomes form oxycodone N-oxide from oxycodone by the flavin-containing monooxygenase as determined by LCMS-MS. Oxycodone N-oxide is chemically stable but in the presence of hepatic microsomes or cytosol, oxycodone N-oxide is rapidly retro-reduced to oxycodone by at least three distinct hepatic protein systems (i.e., quinone reductase, aldehyde oxidase and hemoglobin). To confirm in vitro observations, oxycodone was administered to rats and humans. In both cases, significant amounts of oxycodone N-oxide was formed. Administration of oxycodone N-oxide to rats showed significant amounts of urinary oxycodone and its metabolites and confirmed retro-reduction in vivo.

In this report, it was shown that oxycodone was *N*-oxygenated by human flavin-containing monooxygenase, a hepatic microsomal enzyme. Oxycodone N-oxide was shown to be retro-reduced to oxycodone by at least three enzymatic systems including aldehyde oxidase, quinone reductase and hemoglobin. Oxycodone N-oxide possesses some novel properties in being polar yet sufficiently lipophilic to remain in the endoplasmic reticulum to be converted to oxycodone. Thus, oxycodone N-oxide may serve in a depot effect for metabolic conversion to oxycodone.

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Media contacts: To arrange on-site, phone, or Skype interviews with the researchers involved in this study, please contact John Cashman at (858) 458-9305 / JCashman@hbri.org.

This research was funded by Pain Therapeutics, Inc.

The study was co-authored by Mark Gohdes, Covance Laboratories and Annelies de Kater and Grant Schoenhard of Pain Therapeutics. The paper can be found at:
<https://doi.org/10.1124/dmd.119.089300>

About Human BioMolecular Research Institute

The Human BioMolecular Research Institute is a non-profit research institute conducting basic research focused on unlocking biological and chemical principles related to diseases of the human brain, cardiovascular disease and cancer. The Institute conducts fundamental studies of central nervous system disorders, heart disease and cancer including stem cell approaches and translates findings into new drug development to address human illness. In addition, the Institute

promotes scientific learning through community service and public access by disseminating information and sharing research with collaborators, colleagues and the public. For more information, visit us at www.HBRI.org.

About Pain Therapeutics Inc.

Pain Therapeutics (now Cassava Sciences) is a for-profit company doing research directed at identifying new approaches for addressing human diseases. A key focus of Cassava Sciences is to develop first-in-class medicines for people with debilitating neurodegenerative conditions like Alzheimer's Disease. Another approach is to develop bioanalytical procedures for human diseases. For more information, visit www.Cassavasciences.com.