COMMENTARY

Note on Oxycodone N-Oxygenation and Oxycodone N-Oxide Retro-Reduction

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ABOUT THE STUDY

Oxycodone, oxymorphone and naltrexone are opioids that are N-oxygenated by the Flavin-Containing Monooxygenase (FMO). These drugs are potent Central Nervous System (CNS) agents that previously were thought to be largely metabolized by Cytochrome P450 (CYP) and then in a second step, conjugated in Phase II metabolism [1-4]. A few reports suggested the presence of oxycodone N-oxide as a metabolite but no unambiguous evidence was reported [4-6].

The observation that FMO metabolizes lipophilic tertiary amines such as opioids is not completely surprising. The noteworthy retro-reduction of opioid tertiary amine N-oxide metabolites to the parent tertiary amine is quite significant. Retro-reduction of tertiary amine N-oxides has been reported [7,8]. However, this may be more widespread phenomena that previously recognized. Retro-reduction of tertiary amine N-oxides may have notable consequences for tertiary amine drug metabolism, pharmacokinetics and clinical pharmacology.

FMOs accept nucleophilic, lipophilic tertiary amine substrates and generally convert them to relatively stable, polar, readily excreted tertiary amine N-oxides [9]. Prochiral tertiary amines can be stereoselectively N-oxygenated by FMO [10,11]. The recent report that the major FMO in adult human liver (i.e., FMO_3) forms both H_2O_2 and superoxide anion radical as a result of enzyme uncoupling of the peroxyflavin in the presence of substrate does not detract from the overall observation of considerable stereochemical purity of tertiary amine N-oxide products from prochiral FMO_3 substrates [12]. Currently, there is no evidence that physiologically-derived H_2O_2 or superoxide anion contributes to drug tertiary amine N-oxide formation. Tertiary amine N-oxides can be metabolically retro-reduced to their parent amine [7]. For example, tamoxifen N-oxide is retro-reduced by CYPs and hemoglobin [8]. It is possible that stereoisomeric tertiary amine N-oxide metabolites could be stereo selectively retro-reduced, but to date, there is no evidence for this.

In our recent publication we reported that human liver microsomes formed oxycodone N-oxide from oxycodone as determined by LCMS-MS. Results indicated that oxycodone was N-oxygenated by FMO_3. 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 but not to a detectable extent by CYP or FMO). To confirm *in vitro* observations, oxycodone was administered to rats and humans. In good agreement with *in vitro* results, a significant amount of oxycodone N-oxide was formed. That substantial oxycodone N-oxide was observed in urine after oxycodone administration to rats and humans shows that this previously un-described metabolic pathway is operating in small and large animals.

Administration of oxycodone N-oxide to rats showed significant amounts of urinary oxycodone and its metabolites were formed including noroxycodone, noroxymorphone and oxymorphone *via* CYP. This observation confirmed that oxycodone N-oxide was retro-reduced *in vivo* and oxycodone formed went on and was metabolized.

In summary, our study showed oxycodone was N-oxygenated by human FMO_3. Oxycodone N-oxide was shown to be retro-reduced to oxycodone by at least three enzymatic systems. Oxycodone N-oxide possesses some novel properties: it is polar yet sufficiently lipophilic to remain in the endoplasmic reticulum to be converted to oxycodone [13]. Oxycodone N-oxide may serve in a depot manner for metabolic conversion to oxycodone.

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