Metabolism of Tapentadol–The Data to Date

**Introduction**

- Metabolism may influence drug efficacy and tolerability through drug-drug interactions (DDIs), genetic enzyme polymorphisms, or by generation of pharmacologically active metabolites. 1
- Hepatic metabolism of opioids is primarily carried out by cytochromes (CYP) 450 and uridine 5'-diphospho-glucuronosyltransferases (UGT). 2
- The most commonly prescribed opioids, including codeine, oxycodone, tramadol, and hydrocodone form active metabolites that contribute to both analgesic activity and adverse events (AEs). 2
- Opioids metabolized by CYP450 are associated with clinically important pharmacokinetic drug-drug DDIs. 3
- Co-administration of CYP450 inhibitors may increase opioid serum concentrations, thereby leading to enhanced analgesic and adverse effects. In contrast, CYP450 inducers may lower serum concentrations leading to reduced analgesic activity. 2
- Furthermore, polymorphisms in CYP450 genes, especially CYP3A and CYP2D6, may significantly impact opioid metabolism and can lead to therapeutic failure or toxicity. 4

**Objectives**

- To review the published literature describing tapentadol metabolism and the potential for pharmacokinetic drug-drug DDIs.
- To discuss the potential for interpatient variability in metabolism based on genetic polymorphisms.

**Methods**

- A literature search of MEDLINE®, Pubmed, Embase, and other databases related to the pharmacokinetics of tapentadol was included in this review. 4-10
- The clinical studies that elucidated the pharmacokinetics of tapentadol were included in this analysis. 4-10

**Results**

**Basic Pharmacokinetics of Tapentadol**

- In a phase 1 study involving 4 healthy Caucasian male subjects, a single 100 mg capsule of 3-[14C]-tapentadol HCl was administered orally for the evaluation of the pharmacokinetics of tapentadol in the fasted state. 4
- The concentration of conjugated and un conjugated tapentadol was determined in the serum and urine. 4
- In serum, the majority of tapentadol was in the conjugated form at 1.38 hours, with only a fraction of tapentadol remaining in the unconjugated form (conjugated:unconjugated 41:1). 4
- Excretion was almost exclusively by renal elimination (99%). 4
- In urine, tapentadol, tapentadol-O-glucuronide, tapentadol-O-sulfate, and M1 and M2 metabolites constituted 4.5%, 55%, 15%, 2%, and 13%, respectively of the administered dose in the 24-hour post-dosing period following administration; all metabolites accounted for 99% of the oral dose. 4
- SD: standard deviation, Cmax: maximum serum concentration, mg: mg per mg equivalent. 4

<table>
<thead>
<tr>
<th>Table 1, PK Profile of Tapentadol and IR Formulations</th>
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<td>Tapentadol</td>
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<td><strong>Cmax (ng/mL)</strong></td>
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<td><strong>AUC (ng.h/mL)</strong></td>
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**Fig 1. Cmax for Unconjugated, Conjugated, and Total Tapentadol in Serum**

**Pharmacokinetic DDIs**

- Two randomized, open-label, crossover, DDI studies evaluated the effects of acetaminophen, naproxen, and acetylsalicylic acid on the pharmacokinetics of tapentadol IP. 2
- Co-administration of acetylsalicylic acid or acetylsalicylic acid with tapentadol did not affect its mean serum concentration; the 95% confidence interval (CI) for the ratio of the IP to placebo for Cmax was within the therapeutic range (25-50%). 2
- Co-administration of naproxen did not affect the Cmax of tapentadol. However, the AUC of tapentadol was increased and the 95% CI for the AUC ratio was slightly outside the upper limit of the CI. 2
- The authors conclude that dosage adjustment is not required when coadministered with acetylsalicylic acid, naproxen, and acetylsalicylic acid.

**Population Pharmacokinetics**

- In order to elucidate the association between tapentadol IP pharmacokinetic parameters and demographic characteristics, clinical laboratory values, and disease states, a population pharmacokinetic model was developed using post-dose data from 1827 subjects with moderate to severe pain and healthy subjects. 4

**Discussion and Conclusions**

- Tapentadol is metabolized primarily via glucuronidation. Approximately 85% of an acute oral dose is excreted in the urine as the glucuronide conjugate of tapentadol or its metabolite M2. 2
- Tapentadol is converted to its primary metabolite tapentadol-O-glucuronide by UGT1A1 enzymes, for which there are no reports of genetic variability leading to a poor metabolizer phenotype. 2
- Tapentadol is not a prodrug, and in contrast to the most commonly prescribed opioids, none of the major tapentadol metabolites are pharmacologically active. 2

**References**


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