Liver enzymes, psychotropics, and opioids: Possible reasons for ineffective pain control

The cytochrome P450 (CYP450) liver enzymes are responsible for metabolizing as much as 75% of all drugs administered.[1] Some opioids are pro-drugs relying on the CYP450 system to be activated. Some are dependent on these enzymes to be cleared from the body as expected. If there are changes to levels of key enzymes, it can lead to potential loss of opioid efficacy or toxicity.

Opioids are rarely administered in isolation and many substances can alter the level of CYP3A4 and CYP2D6—both key enzymes in opioid metabolism. Several drugs are well-known as having a potent effect on co-administered drug metabolism, such as rifampin, antifungals, or antiretrovirals. Additionally, Behavioral health medications can have a potent effect on opioid metabolism and thereby complicate pain management.

Substrates, inducers, and inhibitors

A drug can have any of three relationships with a given CYP450 enzyme. It can either be a substrate, an inducer, or an inhibitor. A substrate is a drug which is metabolized by the enzyme. An inducer is a drug which increases the activity of the enzyme. An inhibitor reduces activity.[1] Drugs can also have more than one of these relationships at the same time or have different relationships with different enzymes. The table below provides a breakdown of which opioids and some common behavioral health medications are substrates, inducers, or inhibitors of which CYP450 enzyme. [1,3]

If the drug requires metabolization to be activated, reduced activity via an inhibitor may result in delayed onset and reduced potency. If the drug is active before metabolization, it can mean increased potency and duration. Both could lead to increased accumulation of the administered form and potential toxicity. Two substrates of the same enzyme may also compete for metabolization and effectively reduce the metabolization rate.[1] It is important to note all the listed opioid substrates, in the chart below, require metabolization to activate.

Induction has dissimilar effects. If the drug requires metabolization to be activated, increased activity may result in more rapid onset and increased potency. If the drug is active before metabolization, it can mean decreased potency and duration.

Alternatives

Hydromorphone, morphine, tapentadol, and oxymorphone are not primarily metabolized by the CYP450 system and rely primarily on the glucuronidation pathway.[1,2] These opioids should not be affected by changes in liver enzyme levels. Active metabolites of hydromorphone and morphine may still accumulate with the potential for neuroexcitatory effects if there is reduced kidney function.[2,3] Oxymorphone does not generate any clinically relevant metabolites so would be the safest alternative in this scenario.[3] If CYP450 interactions are suspected, these opioids may be reasonable

alternatives. It is also important to note that a number of over-the-counter (OTC) natural supplements, such as St. John's Wort, may also have a potent effect. Supplements and herbal remedies should always be addressed in a thorough review of medications.

Enzyme	Substrate (opioid)	Substrate (BH medication)	Inhibitor	Inducer
CYP3A4	Codeine Fentanyl Hydrocodone Methadone Oxycodone Tramadol	Alprazolam Aripiprazole Buspirone Carbamazepine Citalopram Diazepam Donepezil Fluoxetine Haloperidol Mirtazapine Nefazodone Trazodone Valproate Venlafaxine Zaleplon Ziprasidone Zolpidem	Diazepam Fluoxetine Fluvoxamine Haloperidol Nefazodone Nortriptyline Sertraline Venlafaxine	Carbamazepine Phenobarbital Phenytoin Valproate
CYP2D6	Codeine Methadone Oxycodone Tramadol	Amitriptyline Amphetamine Desipramine Donepezil Duloxetine Fluoxetine Fluvoxamine Haloperidol Nortriptyline Paroxetine Risperidone Venlafaxine	Bupropion Citalopram Duloxetine Escitalopram Fluoxetine Haloperidol Methadone Paroxetine Sertraline Venlafaxine	No significant inducers

References

1. Holmquist GL. Opioid Metabolism and Effects of Cytochrome P450. Pain Medicine. 2009;10:S20-S29. doi: 10.1111/j.1526-4637.2009.00596.x
2. Tennant F. Making Practical Sense of Cytochrome P450. Practical Pain Management. 2010;10(4). https://www.practicalpainmanagement.com/treatments/pharmacological/opioids/making-practical-sense-cytochrome-p450
3. Smith HS. Opioid Metabolism. Mayo Clin Proc. 2009;84(7): 613–624. doi: 10.1016/S0025-6196(11)60750-7