LEVERAGE OBJECTIVE INFORMATION TO IDENTIFY INTERACTIONS BETWEEN OPIOID ANALGESICS & ANTIDEPRESSANTS

Q: Many of my patients requiring opioid analgesic therapy are also taking medications commonly used to treat depression, anxiety, and other psychological disorders. What kinds of drug-drug interactions (DDIs) are possible between opioid analgesics and antidepressants?

A: Certain drugs used to treat depression and psychological disorders are capable of affecting the body’s ability to metabolize other prescription drugs. Many antidepressants inhibit the action of enzymes responsible for the metabolism of opioid analgesics to their active metabolites, potentially altering the effectiveness of the prescribed pain management medications.

Pharmacokinetic drug-drug interactions can affect the absorption, distribution, metabolism, or excretion of a prescribed medication. A number of opioid analgesics are prone to drug interactions, and consequences can include drug toxicity, decreased efficacy, or potentially death secondary to adverse drug events.1

Kinetic DDIs involving opioids are typically associated with drug metabolism and the CYP450 family of enzymes, with CYP3A4 and CYP2D6 being responsible for the majority of opioid metabolism.2 In general, metabolism by CYP3A4 generates inactive drug products, whereas CYP2D6 produces active compounds.3 Alterations to the activity of either CYP3A4 or CYP2D6 can considerably modify the effect the drug has on the patient and pose a significant problem for practitioners. The CYP2D6 enzyme activity can be decreased (via inhibition) but not increased (via induction), unlike CYP3A4, which is susceptible to both.

Numerous drugs used in the treatment of depression are known to decrease CYP2D6 activity via kinetic inhibition; including paroxetine, sertraline, fluoxetine, and bupropion.4,5 The clinical significance of CYP2D6 inhibition is variable and highly dependent on its role in the metabolism of individual medications. Inhibition can lead to an increase in active parent drug or a decrease in active metabolite. A high-level summary regarding how opioid analgesics are affected by alterations in CYP2D6 metabolism can be seen in the table below.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CYP2D6 METABOLITE (ACTIVE)</th>
<th>EFFECT OF CYP2D6 INHIBITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>Oxymorphone</td>
<td>Potential reduction in analgesic effects1,4</td>
</tr>
<tr>
<td>Codeine</td>
<td>Morphine</td>
<td>Decrease in analgesic effects1,6</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Hydromorphone</td>
<td>Decrease in analgesic effects1,7</td>
</tr>
<tr>
<td>Tramadol</td>
<td>O-desmethyltramadol</td>
<td>Decrease in analgesic effects1,8</td>
</tr>
</tbody>
</table>

Oxycodone is primarily metabolized by CYP3A4 to inactive compounds, but CYP2D6 is responsible for converting oxycodone to oxymorphone, its active metabolite.3 Evidence regarding effects of CYP2D6 inhibition on the analgesic activity of oxycodone is conflicting; due to the fact that both oxycodone and its metabolite are active, providers should be aware of the potential for a reduction in oxycodone effectiveness when concurrent use of a CYP2D6 inhibitor is necessary.9,10
Unlike oxycodone, stronger evidence of reduced analgesia secondary to CYP2D6 inhibition of codeine, hydrocodone, and tramadol metabolism exists. Each of these medications are converted via CYP2D6 metabolism to active metabolites with opioid activity that exceeds that of parent drug. Various clinical trials have validated both reduction in metabolite concentrations and therapeutic effects associated with each of these medications when concomitantly taken with strong CYP2D6 inhibitors. Providers should be aware that co-administration of a strong CYP2D6 inhibitor with codeine, hydrocodone, and tramadol may result in a reduction of expected analgesia at normal dosages, and that dose escalation in patients requiring concomitant use of interacting substance may be required.

Not all opioid analgesics are affected by the CYP450 enzyme family. Morphine, oxymorphone, and hydromorphone are primarily metabolized by phase II conjugation reactions and are at low risk of being influenced by pharmacokinetic DDIs involving CYP450 interactions. These drugs may be potential alternative therapies for patients at risk for or suspected of having DDIs. Additional consideration of potential DDIs should be taken when initiating or titrating the dosage of either antidepressants or pain medications when they are concomitantly prescribed. Understanding the expected alterations in opioid metabolism can have an impact in optimizing medication therapy.

Aegis has developed its Drug-Drug Interaction (DDI) Testing service to deliver information to healthcare providers about interactions like these and help them make informed treatment decisions for their patients. To learn more about the service, go to www.aegislabs.com or contact the Clinical Science team at 877.552.3232 with any additional questions.

REFERENCES: