UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Drug Interactions Review: Opioids & CYP Enzyme Inhibitors

Background:

Opioids metabolized by cytochrome P450 enzymes (codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone) are associated with numerous pharmacokinetic drug interactions that can result in either increased opioid effect or decreased opioid effect.

In this issue, we will focus on pharmacokinetic interactions that affect concentrations/metabolism of these opioids that would put patients at higher risk for unintentional overdose. This is not meant to be an all-inclusive list of drug interactions with opioids.

Opioid Metabolism and CYP Enzymes Involved in Metabolism

Opioid	CYP Enzymes
Codeine	3A4, 2D6 (morphine)
Oxycodone	3A4 (noroxycodone), 2D6 (oxymorphone)
Hydrocodone	3A4, 2D6 (to hydromorphone)
Fentanyl	3A4
Tramadol	3A4
Methadone	3A4, 2B6, 2D6, 2C19

*hydromorphone, morphine not included as metabolism mainly by glucuronidation

Importance:

Many of our patients are prescribed opioids. It is important for palliative care clinicians to be aware of common, clinically relevant drug interactions that may put our patients at risk for unintentional opioid adverse effects.

The Literature:

J Pain Symptom Manage. 2023 Aug;66(2):e307-e309.

Fentanyl toxicity related to concomitant use of ciprofloxacin and its effects as a cyp3A4 inhibitor

Methods: Case report

Results: 40 yo pt with advanced cancer on fentanyl patch prescribed ciprofloxacin for infection developed increased somnolence and myoclonic jerking movements. After discontinuation of ciprofloxacin, symptoms resolved

Discussion:

- Ciprofloxacin is a CYP3A4 inhibitor, which would increase the levels of fentanyl, although NOT noted as a worrisome drug interaction within Lexicomp® database
- It is important to be cognizant of CYP inhibitors, specifically to avoid unwanted ADE of opioids

Am J Manag Care. 2011 Sep;17 Suppl11:S276-287.

Opioid pharmacokinetic drug-drug interactions

- Oxycodone
  - CYP3A4 (~80%) to inactive metabolite
    - Inhibitors: itraconazole, ketoconazole, miconazole, voriconazole, ritonavir, lopinavir, and grapefruit juice have all been shown to increase oxycodone exposure in controlled trials
    - Strong clinical evidence; black box warning exists for concomitant use of CYP3A4 inhibitors and oxycodone
  - CYP2D6 (< 10%) to oxymorphone (active)
    - Inducers and inhibitors of 2D6 have limited effects on plasma concentrations since less is metabolized by 2D6
- Fentanyl
  - CYP3A4 to inactive metabolite
    - Inhibitors: Fluconazole, voriconazole, ritonavir, diltiazem and cyclosporine have been shown to increase fentanyl exposure in clinical trials and case reports
    - Strong clinical evidence; black box warning exists for concomitant use of CYP3A4 inhibitors and fentanyl
- Tramadol
  - CYP2D6 to active metabolite
    - Since both are active, relevancy of CYP2D6 inhibition is not well established
      - Strong inhibitors may produce diminished effect, while weak inhibitors may not be clinically relevant
  - CYP3A4 to inactive metabolite
    - Limited data exists for CYP3A4 inhibitors, although theoretically can increase tramadol levels
- Hydrocodone
  - CYP2D6 to hydromorphone (active)
    - Limited data exists for clinical relevance of inhibitors and inducers of 2D6
  - CYP3A4 to inactive metabolite

J Pain Symptom Manage. 2019 Mar;57(3):635-645.

Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper

- Several CYP450 enzymes involved in methadone metabolism: CYP2B6, CYP2C19, CYP3A4, CYP2D6
- Enzyme inhibition occurs quickly, so can potentially see increase in methadone serum levels and adverse effects within 1-2 days

Table 4
Drug Therapy Modification for Patients on Stable Methadone Dose

Desired Modification	Recommendation
Initiating an inducer	Monitor carefully for increased pain or withdrawal symptoms. Provide breakthrough opioid for pain.
Discontinuing an inducer	Empirically reduce methadone dose by 25%–33%, monitor carefully, and use generous breakthrough (consensus recommendation)
Initiating an inhibitor	Empirically reduce methadone dose by 25% and monitor carefully.
Discontinuing an inhibitor	Monitor carefully for increased pain or withdrawal symptoms. Provide breakthrough opioid for pain.

- Common CYP inhibitors that may increase methadone levels and require dose adjustment of methadone if using together
  - **Anti-infectives**: fluconazole, ketoconazole, itraconazole, ciprofloxacin, erythromycin, troleandomycin, clarithromycin, telithromycin
  - **Antidepressants**: fluoxetine, paroxetine, sertraline, fluvoaxime, citalopram, amitriptyline, desipramine
  - **Amiodarone**

Bottom Line:

- Opioids with highest likelihood of CYP-related drug interactions: methadone, fentanyl and oxycodone
  - Less CYP-related drug interactions with morphine and hydromorphone as they are metabolized via glucuronidation
- Consider the 3 A's (anti-infectives, antidepressants, amiodarone) to remember significant drug interactions with methadone. Also remember this is not an all-inclusive list!
- Ask a pharmacist for recommendations re: clinical relevance of drug interaction and need to adjust doses of opioids in setting of interactions to avoid increased opioid levels
- Opioid metabolism is a growing area of pharmacogenomics research and it is possible that pharmacogenomics play a role in cyp-related drug interactions

CLINICAL PEARL: Morphine and hydromorphone are less likely to have CYP enzyme-related interactions as they are metabolized by glucuronidation