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:

New Medication Review: Roxybond® (abuse-deterrent, oxycodone hydrochloride IR) for severe pain

Background:

Roxybond (oxycodone hydrochloride IR) is the first immediate-release opioid formulation manufactured with abuse deterrent technology. Roxybond® is an opioid agonist indicated for "the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate." It is available as 5mg, 10mg, 15mg, and 30mg immediate release tablets and can be taken orally every 4 to 6 hours as needed for pain.

Importance:

Seriously ill patients have pain and often require opioids as part of the treatment plan. Opioid stewardship is an important component to keeping our patients safe. It is important for palliative care clinicians to be aware of new formulations that may reduce potential for misuse and evidence to support their use in our population.

Pharmacology:

Mechanism of Action	Opioid agonist, binding to opioid receptors in the CNS
Absorption	Similar to oxycodone IR; 60-87% PO bioavailability. High fat meals may increase absorption up to ~20%
Distribution	Distributed to skeletal muscle, liver, intestinal tract, lungs, spleen and brain
Metabolism	Hepatically via CYP3A4, CYP2D6
Excretion	Half-life is 3.8-4.3 hours Primarily excreted in via kidneys

Other Clinical Pearls:

Contraindications	Significant respiratory depression, acute or severe bronchial asthma in unmonitored setting/in absence of resuscitative equipment, hypersensitivity to oxycodone, GI obstruction
Warnings and Precautions	Same warnings/precautions exist for other full agonist opioids
Adverse Reactions	Opioid-related side effects: constipation, nausea, drowsiness, headache, pruritis, dizziness, urinary retention, etc.
Drug Interactions	Avoid co-administration with other CNS depressants may increase risk for CNS depression Co-administration with serotonergic agents may increase risk for serotonin syndrome CYP3A4 inducers may reduce plasma concentration of oxycodone (efficacy or potentiate withdrawal) CYP2D6/CYP3A4 inhibitors may increase plasma concentration of oxycodone; use with caution
Dose Adjustments	Dose reductions may be necessary in setting of reduced metabolism and excretion in setting of liver and/or kidney dysfunction
Other	Schedule II Controlled Substance ***Instruct patients to swallow tablets whole*** ***1:1 conversion from oxycodone IR***

What's the situation with this "abuse deterrent" formulation?

Roxybond is formulated with Sentrybond®, that combines inactive ingredients to protect against physical manipulation, chemical extraction, for intranasal or intravenous use.
If tablets are manipulated, they form a viscous mass when combined with solvents, making it more difficult to administer intravenously

The Literature:

Adv Ther. 2019 Jul;36(7):1730-1740.

Relative oral bioavailability of an abuse-deterrent, immediate-release formulation of oxycodone, oxycodone ARIR in a randomized study

Methods: open-label, randomized, single-dose, three-period, three-treatment, six-sequence crossover study of oxycodone ARIR 30mg and IR oxycodone 30mg under fasting conditions and oxycodone ARIR 30mg under fed conditions

- Naltrexone was administered to block analgesic and psychological effects of oxycodone during the study period
- Blood samples taken within 90 minutes before scheduled dose time and at standard timepoints through 24 hour period

Results: n=58; mean age 25 years old, ~75% male
Safety: adverse effects were typical of opioid-related events and were mild/moderate

Table 2 Summary of pharmacokinetic parameters for Oxycodone ARIR and IR oxycodone

Parameter	Oxycodone ARIR fed[a] (*N* = 58)	Oxycodone ARIR fasted[a] (*N* = 58)	IR oxycodone fasted[a] (*N* = 54)
AUC_{0-t}, ng·h/mL	354.2 (23.3)	287.4 (22.9)	300.3 (22.9)
$AUC_{0-\infty}$, ng·h/mL	361.9 (23.9)	292.7 (23.0)	305.4 (22.9)
C_{max}, ng/mL	68.0 (29.5)	57.8 (31.1)	67.7 (35.1)
T_{max} (h)	2.0 (1.0, 6.1)[b]	1.8 (0.8, 5.0)[b]	1.0 (0.5, 5.0)[b]

ARIR abuse-resistant immediate release, $AUC_{0-\infty}$ area under the plasma concentration–time curve from 0 h and extrapolated to infinity, AUC_{0-t} area under the plasma concentration–time curve from 0 h to last measurable concentration, C_{max} maximum observed plasma concentration, T_{max} time associated with C_{max}
[a] Values are arithmetic means (coefficient of variation percent), except T_{max}
[b] Median (range)

Conclusion: "In this single-dose PK study, Oxycodone ARIR has similar bioavailability to IR oxycodone, and Oxycodone ARIR is expected to have the same efficacy and safety profile as IR oxycodone when taken as indicated. In addition, these data indicate that Oxycodone ARIR can be administered without regard to food."

CLINICAL PEARL: Oxycodone IR (Roxybond®) is a newly approved oxycodone formulation made with inactive ingredients to protect against physical manipulation for intravenous use and as a less favorable option via intranasal route.

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Pain Med. 2019 Apr 1;20(4):747-757.

A randomized, double-blind, double-dummy, placebo-controlled, intranasal human abuse potential study of oxycodone ARIR: A novel, immediate-release, abuse-deterrent formulation

Methods: randomized, double-blind, double-dummy, active- and placebo-controlled, four-way crossover; 1:1:1:1 placebo, crushed IR oxycodone (30mg), crushed oxycodone ARIR (30mg), intact oxycodone ARIR (30mg)

- Inclusion: adults (18-55 years old) who used opioids for nontherapeutic purposes at least 10 times in the preceding year and at least once in the 12 weeks before screening , with three or more instances of using a drug intranasally within the past year
- Exclusion: physical dependence on opioids, participated in/participating in/seeking treatment for substance-related disorders, "positive" UDS during qualification or admission periods

Outcomes:

Primary: Mean maximum drug liking (Emax), as measured by subjects on a bipolar 100-mm Visual analog scale

Secondary: desire to take the drug again, overall drug liking, drug high, and good effects, Pharmacokinetic assessments included peak concentration and time to peak concentration

Results: n=29; mean age 24.4, 83% male, 94% white

- Crushed intranasal oxycodone ARIR demonstrated a significant reduction of 46.9% and 23.4% in drug liking Emax compared with crushed intranasal IR oxycodone and intact oral oxycodone ARIR, respectively ($p < 0.0001$)
- Scores for "overall drug liking" and "take drug again" were significantly reduced for crushed intransal oxycodone ARIR compared with crushed intranasal IR oxycodone or intact oral oxycodone ARIR ($P < 0.0001$)
- Peak plasma concentration was lower for crushed intranasal oxycodone ARIR compared to intact oral oxycodone ARIR and crushed IR oxycodone, both of which had similar peak plasma concentration
- Time to peak plasma concentration was **lower** for crushed intranasal oxycodone ARIR compared to **both** intact oral oxycodone ARIR and crushed intranasal oxycodone IR
- Safety: less adverse events in the crushed oxycodone ARIR group, but similar types of reactions across groups: pruritis, nausea, vomiting

Conclusion

"oxycodone ARIR has the potential to reduce misuse and abuse via the intranasal route of administration"

J Opioid Manag. 2020;16(5):383-390.

In vitro evaluation of a novel immediate-release formulation of oxycodone (Roxybond) for the potential for abuse via injection

- Summary: This study aimed to assess intravenous administration potential of oxycodone ARIR compared to oxycodone IR using in vitro lab studies. It was very difficult to draw any liquid into a syringe for samples containing crushed oxycodone ARIR. Samples containing crushed oxycodone IR were easily drawn into a syringe
- Conclusion: "The difficulty required to prepare an injectable solution from oxycodone ARIR when manipulated suggests that oxycodone ARIR has abuse-deterrent properties that may deter IV abuse"

Discussion:

- Roxybond® when crushed and administered intranasally has a smaller peak plasma concentration and takes longer to get to peak plasma concentration when compared to oxycodone IR tablets
- Roxybond® cannot be crushed, dissolved in solvent and used intravenously due to the "abuse deterrent" formulation
- Overall, drug liking was lower for intact Roxybond® than crushed oxycodone IR, but not as low as crushed Roxybond.® What I find really interesting is that intact Roxybond® has similar peak plasma concentrations and time to peak levels as crushed oxycodone IR. This makes it clear that although it might be less favorable to manipulate the formulation to use intranasally or intravenously, one could still misuse the tablet by oral route (the intended route of administration). Likely leading to the statement on the manufacturer's website that "*RoxyBond abuse is still possible by intranasal, intravenous, and oral routes"*
- Also, I'd be remiss to not mention the questionable study methods from an ethical standpoint (?)
- It is unclear how the peak plasma concentrations relate to analgesic efficacy and it has not been compared to other oxycodone products for these outcomes…
- This formulation has same opioid "class" side effects
- It does not appear that this medication can be split in half, which would possibly make it more difficult for some of our patients with dysphagia to use or be more restrictive with dosing than other IR formulations
- Highest tablet strength is 30mg which may pose limitations for our patients, especially with cancer, who require higher PRN doses
- Wholesale Acquisition Cost: $17-31 per tablet, depending on strength
    - At UPMC, Roxybond® is non-formulary
    - Roxybond® Copay Card is available through the website for discounted co-pays for those with commercial insurance

CLINICAL PEARL: Oxycodone IR (Roxybond®) is a newly approved oxycodone formulation made with inactive ingredients to protect against physical manipulation for intravenous use and as a less favorable option via intranasal route.