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:

Transmucosal Drug Delivery: A Focus on Opioids

Background:

Traditional oral opioids are not always a suitable option for our patients, especially those with dysphagia issues or at end of life. Transmucosal drug delivery can be an option in these instances and includes buccal, sublingual (SL), and translingual formulations. Buccal: insert medication between cheek and tongue and allow to fully dissolve; Sublingual: place medication under tongue and allowing to fully dissolve; Translingual: apply medication to top of patient's tongue.
Transmucosal drug delivery can be an option for opioids, although commercially available transmucosal products are scarce, except for fentanyl.

Fentanyl comes in a variety of transmucosal formulations, given its highly lipophilic nature: Subsys®, Actiq®,Fentora®, and Abstral®. They are rapidly absorbed (~25-50%) from the transmucosal, although about 50-75% is swallowed with saliva and slowly absorbed in GI tract. Bioavailability (BA) of these products has been well-documented and ranges between 50-75%. An ideal time to keep buccal lozenges (Actiq®) in the mouth for optimal absorption is 15 minutes. Unfortunately many of these fentanyl products are expensive, require prior authorizations, require patients to be opioid tolerant or require adherence to Risk Evaluation and Mitigation Strategy (REMS) Programs, so are used sparingly in clinical practice.

No other opioids (besides buprenorphine) come in transmucosal formulations, but we commonly use concentrated liquids of morphine and oxycodone for sublingual administration. Extent of absorption is limited by characteristics of the medication including ionization and lipophilicity. Did you ever wonder how and to what extent these are absorbed or how they should be administered for optimal absorption? Read on!

Importance:

We often utilize concentrated liquid opioids for pain control in patients without PO availability. Palliative care clinicians should be aware of the pharmacokinetic considerations and expectations of commonly prescribed opioids to make decisions surrounding dose escalation, opioid rotation, or patient education.

The Literature:

Pain Med. 2014 Jul;15(7):1129-53.

Alternative routes to oral opioid administration in palliative care: A review and clinical Summary

- Lipophilic medications like fentanyl and methadone are well absorbed in oral cavity
- Hydrophilic medications like oxycodone, hydromorphone, and morphine are poorly absorbed so most of their efficacy is a result of the medication being swallowed

Sublingual

- PK data previously indicated that blood levels of morphine, oxycodone, and hydromorphone following SL administration did not rise faster than those following oral administration
- Must retain medication for *several minutes* sublingually for optimal chance of absorption

1st author, year	Study design	Regimens studied	Summary of results
Weinberg, 1988	Observational, (10-35 healthy patients)	SL methadone, fentanyl, buprenorphine, morphine	SL absorption of methadone at a pH of 6.5 was 34%. SL absorption and BA of morphine is poor; highly lipophilic medications demonstrate better BA.
Hagen, 2007	Open-label (n=7)	SL methadone	Median time to analgesic onset/time to meaningful pain reduction within 5 minutes of administration. Six of the seven patients asked to continue using sublingual methadone following the trial.
Hagen, 2010	Feasibility (n=9)	SL methadone	Mean pain intensity dropped by 1.7 points (on a 10-point numerical scale) within 10 minutes of SL methadone, and by 3.2 points after 15 minutes.
Gupta, 2010	Case study (n=1)	SL methadone	SL methadone appears to be a suitable alternative to IV and topical administration in the treatment of mucositis-related pain.

Buccal

1st author, year	Study design	Regimens studied	Summary of results
Beyssac, 1998	Cross-over (n=12)	Morphine buccal (30mg CR tab vs. 20mg aqueous solution retained in mouth for 10 mins vs. 60mg buccal tablet for 6 hours)	10% of morphine dose absorbed. Plasma levels for the buccal tablet similar to oral controlled-release tablet; bioavailability of the buccal tablet ~ 98% compared with the controlled-release tablet
Kokki, 2006	Randomized, open label (n=15, children)	Oxycodone buccal (parenteral liquid, 10mg/mL)	Cmax ranged from 5.4 to 39 ng/mL (median 16 ng/mL) with 12 of the 15 children reaching the oxycodone analgesic concentration of 12 ng/mL, which was sustained for average of 2.5 hours. Tmax ranged from 30 to 120 minutes (median 60 minutes)
Kokki, 2004	Prospective, open (n=40, children)	Oxycodone IV, IM, buccal, or gastric administration (10mg/mL)	Peak concentration for buccal administration was much lower than IV administration Time-to-peak concentration was ~3.5 hours (avg) for buccal compared with ~15 mins (avg) for IV Est. BA of buccal oxycodone was calculated to be ~50% (avg)

CLINICAL PEARL: Bioavailability varies for transmucosal route of administration based on lipophilicity and ionization of medications. More lipophilic, the higher bioavailability.

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The Literature Continued…

Clin Pharmacol Ther. 1988 Sep;44(3):335-42.

Objective: To estimate the absorption of selected opioids from the SL space under conditions in which swallowing was controlled

Methods: between 10-35 healthy subjects; holding medications under tongue for 10 mins (without swallowing)

Results:

- Methadone, fentanyl, buprenorphine were absorbed to a significantly greater degree than morphine, whereas oxycodone, hydromorphone were not

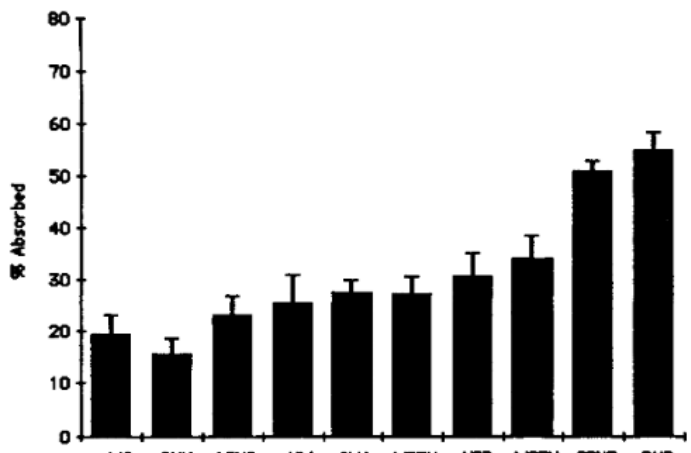

Fig. 1. The mean absorption (+SE) of the test opioids after 10 minutes in the oral cavity of normal subjects (n = 10 for each test condition). The pH of the dosing solution was 6.5. *MS*, morphine sulfate; *OXY*, oxycodone; *LEVO*, levorphanol; *HM*, hydromorphone; *NAL*, naloxone; *METH*, methadone; *HER*, heroin; *FENT*, fentanyl; *BUP*, buprenorphine.

- Time in oral cavity for methadone and fentanyl impacted absorption (more absorption after 10 mins versus 2.5 mins); no difference for buprenorphine
- SL bioavailability of morphine ranged from 0-31%, mean of 9% +/- 11.9%

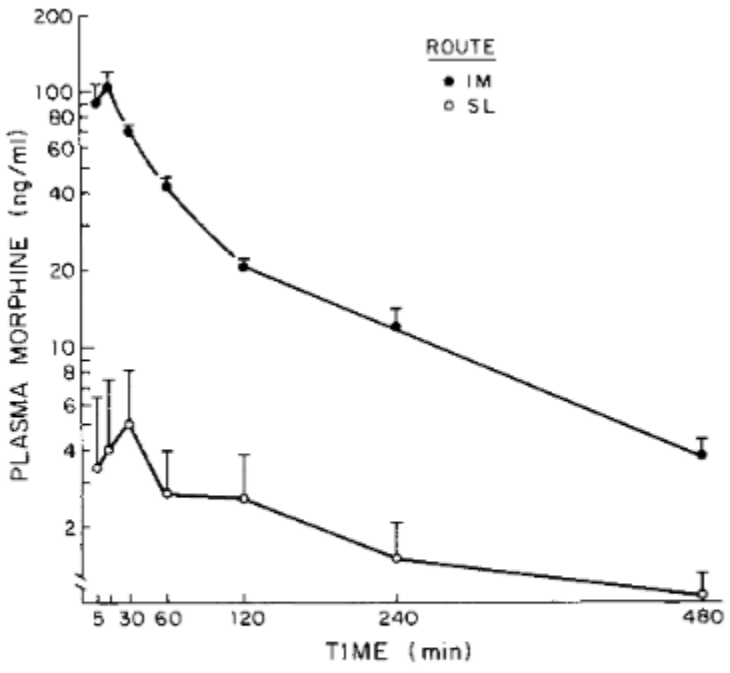

Fig. 4. Plasma morphine concentration-time profiles (+SE) after intramuscular *(IM)* or sublingual *(SL)* administration of 15 mg morphine sulfate to seven normal subjects.

Several Fast Facts Describe Transmucosal Routes of Opioids:

- Fast Fact 358: Non-oral routes of methadone
- Fast Fact 53: Sublingual morphine

Bottom Line:

- It is safe to administer opioids that are not commercially available as SL or buccal form in this way by using concentrated oral solution
- Bioavailability of hydrophilic opioids (morphine, oxycodone, and hydromorphone) is much less than lipophilic opioids
- SL methadone is effective quickly, given its lipophilic nature
- Transmucosal doses may be limited based on volume constraints
- Some analgesic benefit is reliant on absorption in GI tract when swallowing liquid with saliva. This may matter for patients who have undergone resections of GI tract or have short-gut syndrome…
- It may take several minutes (up to 10 minutes) for the medication to be completely absorbed transmucosally, which seems reasonable but in real-life scenarios this may not be feasible

CLINICAL PEARL: Bioavailability varies for transmucosal route of administration based on lipophilicity and ionization of medications. More lipophilic, the higher bioavailability.