Intranasal Medication Use in Palliative Care

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Objectives

• Review Benefits of IN Medication Delivery
• Medication Qualities for effective IN administration
• Fentanyl and Sufentanil
• Ketamine and Midazolam
• Pharmaceutical products available for use
Rationale for IN Medication

• The young physician starts life with 20 drugs for one disease and the old physician ends life with one drug for 20 diseases

William Osler
IN Medications

• Use in patients with nausea and vomiting
• Use in patients unable to swallow, with mucositis or poor saliva production
• Ease of administration and patient acceptance of method
• Rapid onset of action
• Avoidance of GI and hepatic first-pass effect
• Relatively cheap to provide
• Painless
• Can titrate dose to individual patient needs
IN Limitations

- Requires intact nasal mucosa for maximal effect
- Small absorption surface
- Absorption limited by mucocilliary clearance
- Medication must be delivered in a manner that maximizes rapid absorption
Pharmacokinetics

- **Absorption** (first pass metabolism, nasal anatomy)
- Distribution
- Metabolism
- Elimination
Nasal Anatomy

Grassin-Delyle, S. et al 2012
Ideal IN Characteristics for Maximal Absorption

- Low MW
- High Lipophilicity
- Zero net charge at physiological pH
- Soluble enough to enable delivery of an effective dose in volume of 100 uL per nostril
IN Medication Breakdown

• Mucociliary clearance and tight junctions

• Nasal endothelial enzymes creating ‘first pass effect’ (not fully understood)

• Strategies to improve bioavailability: prodrugs, excipients, enzyme inhibitors, drug concentration and volume given
Bioavailability

• Limited by the amount of volume delivered to the nasal mucosa

• Ideally 0.2 - 0.6 ml in each nostril; will be dependent on concentration of medication being given

• Atomized medication with rapid delivery
Patient Factors

- Mucociliary transport (eg. CF, intubated patients)
- Diabetic patients
- Hypertrophy in lower turbinate zone (rhinosinusitis)
- Allergic or infectious nasal conditions
- Medications that effect nasal blood flow
- XRT to face and head
IN Opioid Use

• Indication: acute or chronic pain caused by surgery, trauma or cancer

• In patients with cancer mainly for breakthrough pain, possible use for dyspnea

• Most opioids have similar MWs and pKa, but differ greatly in lipophilicity
Pharmacokinetic Properties of Opioids


<table>
<thead>
<tr>
<th>Drug</th>
<th>Log P</th>
<th>MW (Da)</th>
<th>pKa</th>
<th>Relative analgesic potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.76</td>
<td>285</td>
<td>7.9</td>
<td>PO: 1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>0.82</td>
<td>315</td>
<td>8.3</td>
<td>IV/IM: 4</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>0.83</td>
<td>301</td>
<td>8.5</td>
<td>2</td>
</tr>
<tr>
<td>Codeine</td>
<td>1.14</td>
<td>299</td>
<td>7.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>1.63</td>
<td>357</td>
<td>8.3</td>
<td>1</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>1.76</td>
<td>376</td>
<td>8.1</td>
<td>50-200</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.84</td>
<td>285</td>
<td>8.5</td>
<td>5</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>1.92</td>
<td>341</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Alfentanil</td>
<td>1.98</td>
<td>417</td>
<td>6.5</td>
<td>10-20</td>
</tr>
<tr>
<td>Naloxone</td>
<td>2.09</td>
<td>327</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>2.17</td>
<td>299</td>
<td>8.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Pethidine</td>
<td>2.54</td>
<td>247</td>
<td>8.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>3.77</td>
<td>327</td>
<td>8.6</td>
<td>20</td>
</tr>
<tr>
<td>Methadone</td>
<td>3.93</td>
<td>309</td>
<td>8.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>3.95</td>
<td>388</td>
<td>8.0</td>
<td>500-1000</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>4.05</td>
<td>336</td>
<td>8.4</td>
<td>50-100</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>4.98</td>
<td>468</td>
<td>8.4</td>
<td>40</td>
</tr>
</tbody>
</table>

Log P corresponds to the logarithm of the ratio of the concentrations of the studied compound in octanol and in water: Log P = Log (C_{oct}/C_{water}). Values were calculated with the XLogP3 published algorithm (Cheng et al., 2007; Tetko et al., 2005).

* Pure antagonists.
* Partial µ receptors agonist.
“A transient exacerbation of pain that occurs either spontaneously or in relation to a specific or an unpredictable trigger despite relatively stable and adequately controlled background pain”

- Rapid onset (1-3 mins)
- Moderate to severe intensity
- Relatively short duration (30-60 min)
- Occurs in 80-90% of patients with advanced cancer
- Associated with lower quality of life, higher distress, more severe pain
IN Fentanyl

• Highly lipophilic and low MW
• Good absorption; not necessary to use absorption promoters or solid/mucoadhesive formulations
• 50-100 times higher analgesic activity than morphine
• 2 marketed solutions: Instanyl (aqueous), PecFent (pectin-based mucoadhesive)
Figure 4. Response rates with intranasal fentanyl spray (INFS) (pooled doses) versus placebo for pain reduction by (A) >33% and (B) >50% over time. $P < 0.001$ for all comparisons.
Figure 3. General impression (GI) of efficacy in the treatment of breakthrough pain with (A) intranasal fentanyl spray (pooled doses) (747 treated episodes) and (B) placebo (249 treated episodes). GI was assessed 60 minutes after administration of study medication using a categoric 5-point visual rating scale (0 = poor; 1 = fair; 2 = good; 3 = very good; and 4 = excellent).
BTP Fentanyl versus Placebo

Vissers, et al 2010

*PID = pain intensity difference – a positive value reflects an improvement; INFS = intranasal fentanyl spray; OTFC = oral transmucosal fentanyl citrate; FBT = fentanyl buccal tablet; OM = oral morphine.
INFS for BTP

Vissers, et al 2010

*PID = pain intensity difference – a positive value reflects an improvement. INFS = intranasal fentanyl spray; OTFC = oral transmucosal fentanyl citrate; FBT = fentanyl buccal tablet; OM = oral morphine.
Comparison to Buccal/SL Fentanyl

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Onset, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral morphine or oxycodone</td>
<td>30–45</td>
</tr>
<tr>
<td>OTFC</td>
<td>15–30</td>
</tr>
<tr>
<td>FBT</td>
<td>15–30</td>
</tr>
<tr>
<td>SLF</td>
<td>15–30</td>
</tr>
<tr>
<td>INFS</td>
<td>10–15</td>
</tr>
</tbody>
</table>

FBT fentanyl buccal tablets, INFS intranasal fentanyl, OTFC oral transmucosal fentanyl citrate, SLF sublingual fentanyl

Mercadante Curr Pain Headache Rep (2011)

Smith, H. CNS Drugs (2012); 26 (6): 509-535
Instanyl

- Pilot study demonstrated administration of 50 ug resulted in Tmax of 5 minutes with 71% bioavailability
- 19 cancer patients with BTP; Tmax 12-15min
- 2 dbl-blind, placebo controlled RCTs confirmed Tmax of 10min for IN Instanyl
- Pain intensity decreased by 30% within 10 minutes in 58% of IN Fentanyl users; significant pain relief within 5 minutes
PecFent

• Pectin mucoadhesive used to improve bioavailability by increasing contact time with mucosa; must first diffuse within gel

• Pectin Tmax 20 minutes with bioavailability of 133%

• Formulations with higher viscosity (poloxamer, pectin) have longer Tmax and slightly lower bioavailability
Which IN Fentanyl to use?

- In aqueous solution, all fentanyl diffused in approximately 10 min, whereas less than 40% if fentanyl in pectin gel diffused after the same period of time.

- Diffusion of pectin formulation was only 90% complete after 3 hrs; therefore higher doses are required for pectin gel over aqueous solutions.
Generic IN Opioids

• Can deliver fentanyl using a syringe and device to atomize solution

• Bioavailability is contingent on adequate volume and concentration

• Sufentanil may be the better option for adult patients given higher concentration in smaller volume
Generic IN Opioid

Harlos, M.
intranasal.net
IN Sufentanil

• Sufentanil is 10 times more potent than fentanyl; allows use of smaller volume delivered at equianalgesic dose
• Small number of case studies and prospective studies demonstrating similar efficacy for analgesic relief
• No significant adverse effects noted
IN Sufentanil

Figure 1  Median pain VRS over time.

### Protocol for Titration

**If pain is adequately controlled at any point during this phase,** then the number of spray administered should be used all at the same time for the next breakthrough pain spell to determine if in fact it is adequate and safe. If too much sedation occurs – back off by 1-2 sprays until the safe and effective dose is found. If effective 75% of the time or more – this is the dose the patient should use for all further breakthrough pain spells.

**At 30 minutes if pain is not controlled,** provide usual breakthrough pain medication and wait until next spell of breakthrough pain – using Phase II

<table>
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<tr>
<th>Procedure</th>
<th>Volume</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single spray each nostril at onset of pain (time zero)</td>
<td>0.2ml</td>
<td>10mcg sufentanil/100mcg fentanyl</td>
</tr>
<tr>
<td>Single spray each nostril at onset of pain (time 10min)</td>
<td>0.2ml</td>
<td>10mcg sufentanil/100mcg fentanyl</td>
</tr>
<tr>
<td>Single spray each nostril at onset of pain (time 20min)</td>
<td>0.2ml</td>
<td>10mcg sufentanil/100mcg fentanyl</td>
</tr>
</tbody>
</table>
Adverse Effects

- Epistaxis, nasal wall ulcers, rhinorrhea, throat irritation, dysgeusia, nausea, headache
- Contraindications to use: recurrent epistaxis, previous XRT to face
Effect of Rhinitis

• Viral or allergic rhinitis does not alter Instanyl absorption but decreases in absorption by 20% in local vasoconstrictors

• Use of IN fentanyl is not advisable in context of nasal congestion and treatment with vasoconstrictor

• Further study required to determine if PecFent is altered by rhinitis since rhinitis typically affects IN Ca and pectin acts on Ca
Intranasal Ketamine

• Used for pain relief and sedation
• NMDA receptor antagonist; role in neuropathic pain
• Given IV, IM or oral route; IV solution can be given as IN formulation
• Low doses (10mg -50mg IN) required for effective pain relief
IN Ketamine


[Graph showing change in NPIS from baseline over time for Ketamine and Placebo groups with asterisks indicating statistical significance.]

- Ketamine
- Placebo
IN Benzodiazepines

• Studied for both sedation and seizure control
• No studies of use at end of life for these symptoms
• Good evidence to suggest effectiveness at treating seizures; cause minimal sedation
• Be aware of the concentration of midazolam (5mg/ml); may be ineffective to stop seizure activity with one dose
References


References


References


• Personal communication, Dr. Michael Harlos; August 2nd, 2012

• Harlos, M. Intranasal medication <http://www.intranasal.net/> 15 Sept 2012.