Intranasal Medications

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Medical Director, WRHA Adult and Pediatric Palliative Care
• The presenter has no conflict of interest to disclose

• The intranasal use of all medications mentioned in this presentation is “off-label” – i.e. without formal approval or indication by Health Canada / FDA
Objectives

• to review the role of intranasal medication administration in palliative care

• to compare the known pharmacokinetic data of intranasal vs other routes

• to consider advantages of intranasal vs buccal/subling routes
**Some Definitions**

- *lipophilic* – capable of dissolving, of being dissolved in, or of absorbing lipids (Stedman’s Medical Dictionary)
- membranes such as the nasal mucosa or the blood-brain barrier have a lipid bilayer; drugs that are lipophilic can cross membranes more quickly

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**Structure of the Cell Membrane**

- Lipid Bilayer
  - Outside of cell
  - Inside of cell (cytoplasm)
  - Proteins
  - Carbohydrate chains
  - Transport Protein
  - Phospholipids
• **bioavailability** – the proportion of the administered dose that ends up in the bloodstream
  - intravenous is considered 100%
  - often lower by the oral route due to *first-pass metabolism*: drug is absorbed through gut and undergoes metabolism in the liver prior to reaching the systemic circulation

• **intranasal** – it goes here:
Approach To Considering A Medication For Intranasal Use

1. Is there a need? Are there alternative routes that aren’t “off-label”?

2. Is there published evidence for effectiveness? safety and tolerability?

3. In the absence of published evidence evidence:
   • does it make sense pharmacologically?
     – lipid-soluble, small molecular size – e.g. glycopyrrolate does not make sense pharmacologically (quaternary ammonium compound)
   • can its effects be judged empirically?
     – compare a sedative (straightforward to assess beneficial and adverse effects empirically) with dexamethasone (difficult to know whether a poor response reflects the illness, the medication dose, or the route)
   • is there any irritation when administered?
Intranasal Drug Delivery

- non-invasive, simple, well tolerated (depending on the medication – e.g. midazolam is irritating)
- rapid onset – directly through nasal mucosa into systemic circulation
- higher bioavailability than oral – bypasses first pass hepatic metabolism
- lipophilic, small molecular weight drugs best absorbed
- pH will influence ionization of drug (depending on its pKa – how readily it gives up an H+) , which will influence lipophilicity and therefore absorption
- potentially circumvent blood-brain barrier (olfactory region)
Locally acting drugs

Figure. Drug delivery to the CNS from nasal formulations. CNS, Central Nervous System; BBB, Blood Brain Barrier

CNS drugs


Fig. 2 Schematic presentation of differences in the sites of fentanyl absorption in relation to different routes of non-intravenous fentanyl administration.
Advantages Of Intranasal Route Over Buccal / SL

• with buccal/SL, patient is expected to avoid swallowing for 5-10 minutes – not an easy task, and not realistic in cognitive impairment or in younger children
• inconsistent adherence to instructions leads to inconsistent drug effectiveness
• buccal / SL meds may add to secretions (e.g. ALS)
• if swallowed, bioavailability diminishes significantly due to first-pass metabolism
• potential for direct passage into CNS with intranasal
<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_{\text{max}}$ (min)</th>
<th>Bioavail. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>midazolam$^{1,2}$</td>
<td>11 – 14 (effect onset 2 min$^5$)</td>
<td>55 – 83</td>
</tr>
<tr>
<td>fentanyl$^{3,7}$</td>
<td>5-13 (therapeutic levels in 2 min)</td>
<td>71 - 89</td>
</tr>
<tr>
<td>sufentanil$^3$</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>hydromorphone$^4$</td>
<td>20</td>
<td>55</td>
</tr>
<tr>
<td>ketamine$^6$</td>
<td>20</td>
<td>45 - 50</td>
</tr>
<tr>
<td>lorazepam$^8,11$</td>
<td>30 (special prep) – 104 (IV injectable)</td>
<td>78</td>
</tr>
<tr>
<td>haloperidol$^9$</td>
<td>15 (= IV; &gt; twice as fast as IM)</td>
<td>64</td>
</tr>
<tr>
<td>scopolamine$^{10}$</td>
<td>22</td>
<td>83</td>
</tr>
</tbody>
</table>


**Reasonable to start with recommended mg/kg for IV dosing and adjust empirically**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Intrasal</th>
<th>Buccal</th>
<th>IM</th>
<th>PO</th>
<th>IV</th>
<th>SC</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>( T_{\text{MAX}} ) (minutes)</td>
<td>Bioav (%)</td>
<td>( T_{\text{MAX}} )</td>
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<td>( T_{\text{MAX}} )</td>
<td>Bioav</td>
</tr>
<tr>
<td>midazolam</td>
<td>11-14 (onset 2 min)</td>
<td>55-83</td>
<td>30</td>
<td>25</td>
<td>24 - 50</td>
<td></td>
</tr>
<tr>
<td>fentanyl (INJ)</td>
<td>5-13 (therapeutic levels in 2 min)</td>
<td>71-89</td>
<td>51</td>
<td>33</td>
<td>6</td>
<td>10-30</td>
</tr>
<tr>
<td>morphine (*) (add approx 8-10 min to ( T_{\text{MAX}} ) for peak CNS effect)</td>
<td>No data on IV solution</td>
<td>24</td>
<td>20</td>
<td>30-90</td>
<td>30-40</td>
<td>4.8</td>
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<tr>
<td>hydromorphone</td>
<td>20</td>
<td>55</td>
<td>25</td>
<td>60</td>
<td>51</td>
<td>onset 5 min; peak 20</td>
</tr>
<tr>
<td>ketamine</td>
<td>20</td>
<td>45-50</td>
<td>5</td>
<td>25</td>
<td>17</td>
<td>onset 15</td>
</tr>
<tr>
<td>lorazepam</td>
<td>30</td>
<td>78</td>
<td>30-480</td>
<td>6</td>
<td></td>
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</tr>
<tr>
<td>haloperidol</td>
<td>15 (= IV; &gt; twice as fast as IM)</td>
<td>64</td>
<td>20</td>
<td>120-360</td>
<td>60-70</td>
<td>5-15</td>
</tr>
<tr>
<td>scopolamine</td>
<td>22</td>
<td>83</td>
<td></td>
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</tbody>
</table>
Drug Administration In Crisis

- potential crisis situations in palliative care include:
  - severe pain – e.g. pathological fracture
  - severe dyspnea – airway obstruction, superior vena cava syndrome, pulmonary embolism, hemoptysis
  - acute head and neck or GI bleed

- circulation to extremities and subcutaneous tissues often compromised in such situations – cold, clammy, mottled, “shocky”

- there is no pharmacological data on the subcutaneous absorption of common palliative drugs in these circumstance – almost certainly impaired

- my route preference: IV > intranasal > IM > buccal > enteral
Practical Considerations

• “The maximum volume to avoid run-off into the pharynx by a single administration in one nostril in man is 0.15 ml”
  

• other references indicate up to 0.2 ml

• in practice, we give up to 0.5 ml per nostril; this is also described in a protocol in:
  

• the correct dose is “the one that works” – may need some experimentation to find effective dose
Contraindications

- existing contraindications to the specific medication being given (e.g. allergy)
- nasal trauma
- recurrent epistaxis
- congestion, obstruction preventing administration of drug
  - however – allergic rhinitis has been shown not to affect absorption, although treatment with nasal vasoconstrictors does
- previous facial radiation treatment (stated in one publication)
Fentanyl

- highly potent opioid – small volumes needed
- lipophilic – absorbed readily through transmucosal membranes and blood-brain barrier
- increasing pediatric and adult literature on intranasal use of the injectable preparation for pain and dyspnea management
Intranasal Fentanyl

- $T_{\text{MAX}}$ 5 – 15 min.
  - compare with $T_{\text{MAX}}$ of 138 minutes for buccal morphine
- therapeutic levels reported as short as 2 minutes
- bioavailability nasally 71 – 89%
- bioavailability if swallowed: 33% – should avoid swallowing due to diminished effectiveness
- not irritating to the nasal mucosa
A Specific Safety Consideration

- fentanyl or sufentanil often given for incident pain
- one common scenario would be prior to patient transport for investigations (e.g. XRay for path #) or treatment
- should not “squirt-and-go” – patient should be accompanied by someone who can recognize and manage opioid overdose, at least if this is a new treatment approach for the patient
Intranasal Fentanyl for Pain Management in Children: A Systematic Review of the Literature


- intranasal fentanyl equivalent or superior to po/IV/IM morphine & equivalent to IV fentanyl
- strong safety profile
- easily available in the hospital setting
- does not require additional pharmacy compounding
- this strong evidence, along with the significant ease and simplicity of administration potentially superior option and/or adjunct treatment for acute and procedural pain control in children
Safety of Intranasal Fentanyl in the Out-of-Hospital Setting: A Prospective Observational Study

Anders P. H. Karlsen, BM; Danny M. B. Pedersen, EMT; Sven Trautner, MD; Jørgen B. Dahl, MD, PhD; Morten S. Hansen, MD

Ann Emerg Med. 2013

• prospective observational study of IN fentanyl (50 or 100 mcg) administration by paramedics
• N = 903 patients 7+ yrs old with severe abd or orthopedic pain, or acute coronary syndrome refractory to nitroglycerin spray
• median reduction in pain score of 3 out of 10; 79% had a reduction of at least 2 (considered clinically relevant)
• 36 patients experienced adverse effects – none serious
  – most common: ↓ BP (mean drop of 3.5 mm Hg)
  – no resp depression
Brief Report

Intranasal Fentanyl in the Palliative Care of Newborns and Infants

Michael S. Harlos, MD, CCFP, FCFP, Simone Steneke, RN, MN, CHPCN(C),
David Lambert, MD, FRCP(C), Chris Hohl, MD, FRCP(C), and
Harvey Max Chochinov, MD, PhD, FRSC

Palliative Medicine Section (M.S.H.), Faculty of Medicine (M.S.H., H.M.C.), and Department of
Anesthesiology (D.L.), University of Manitoba; Winnipeg Regional Health Authority Palliative Care
(M.S.H.) and Winnipeg Regional Health Authority Pediatric Palliative Care (M.S.H., S.S., D.L.,
C.H.); Department of Pediatric Anesthesiology (D.L.) and Department of Pediatrics (C.H.), Winnipeg
Children’s Hospital; and Manitoba Palliative Care Research Unit (H.M.C.), CancerCare Manitoba,
Winnipeg, Manitoba, Canada

• the only publication describing the use of intranasal fentanyl in newborns
Intranasal Medication Administration by Mucosal Atomization Device (MAD®)

PURPOSE:

Intranasal drug delivery offers a non-invasive alternate route for medication administration. MAD® delivers a fine mist of soluble medication particles to achieve efficient and effective drug levels by direct absorption across the nasal mucosal membranes into the bloodstream.

Atomization offers superior effect compared to drops or sprays.

The absorption rate and plasma concentration of atomization is comparable to intravenous administration (Knoester et al, 2002)
INSTRUCTIONS FOR USE:

1. Physician order required.
2. Explain procedure and expected outcome to patient and family.
3. Fill syringe with prescribed amount of medication solution using the most concentrated form of the medication available. **
4. Connect the MAD® (nasal sprayer) to the syringe via luer lock mechanism
5. Inspect the nostril for significant amounts of blood or mucous discharge. Presence of these discharges will limit mucosal absorption. Suction the nasal passage prior to medication delivery or consider alternate administration route. Lean head back slightly or lay flat.
6. Place the tip of the MAD® in the nostril
7. Squirt half of the medication into each nostril. Splitting the dose doubles the available mucosal surface area for drug absorption and increases the rate and amount of absorption.
8. Rinse MAD® with clean, running water, allow to dry between uses (may reuse for same patient).

** The *ideal* volume for intranasal administration is 0.2-0.3ml and the maximum recommended volume per nostril is 1ml. If dose is greater than 0.5ml, apply it in two separate doses allowing 5-10 minutes apart for each dose. The spacing allows the former dose to absorb.

The MAD® atomizer has a dead space of 0.1ml, so particularly for doses less than 0.9ml be sure to take the dead space into account by adding 0.1ml to the final volume (i.e. volume of dose + 0.1ml)