Topical Opioids: The "Solution" to the Opioid Epidemic

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Disclosures

- Nothing to disclose
Learning Objectives

- Summarize current literature supporting topical opioid administration for pain
- Describe the pharmacokinetic and pharmacodynamic properties of topical morphine
- Identify medical staff and patient/family education needs and implementation strategy
- Explore logistics of adding topical morphine to a health system formulary, establishing medication prescribing guidelines, developing of an order set in electronic health record, and identifying a list of approved prescribers

Outline

- General Topical Medications
- What Exists Now: Topical Opioids
- EBM Publications
- Patient Cases
- Logistics: Formulary, Guidelines/Policies, Compounding, Dispensing
- Safety and Monitoring
Opioid commission tells Trump to declare state of emergency

Examples of Commercially Available OTC Topical Analgesics
Common Rx Topical Pain Agents

- Amantadine (5-20%)
- Amitriptyline (2-10%)
- Baclofen 2%
- Bupivacaine (2-5%)
- Carbamazepine 5%
- Clonidine (0.1-0.3%)
- Cyclobenzaprine (1-3%)
- Dextromethorphan (5-10%)
- Diclofenac (1-10%)
- Gabapentin (5-10%)
- Guaifenesin (10-40%)
- Ibuprofen (10-40%)
- Indomethacin (10-40%)
- Ketamine (5-10%)
- Ketoprofen (10-50%)
- Lidocaine (2-10%)
- Loperamide 1%
- Nifedipine (2-16%)
- Orphenadrine (5-10%)
- Piroxicam (0.5-2%)
- Tetracaine (0.5-10%)
- Topiramate 1%

Transdermal Treatment

- Transdermal delivery allows drugs to solubilize in order to penetrate the tissue layers
- Gels form liposomes that carry the drug down between the cells of the dermis and epidermis
- Minimizes side effects by delivering drug to the site of injury
- Research confirms peripheral site of action for many of these drugs
Current Data

- Several small case series have shown rapid relief using topical opioids in patients with pain due to skin infiltration of tumor, skin ulcers of malignant and nonmalignant origin, several oral mucositis, and knee arthritis.
- Monitoring and drug interactions of topical opioids is same as systemic opioids (excess sedation, respiratory depression, pruritus).


Theoretical Mechanisms of Action

- Topically applied opioids have provided effective analgesia without adverse effects in adult patients with painful inflammatory conditions.
- The presumed mechanism of action is by interaction with opioid receptors that are sited on sensory nerve terminals, and which may be upregulated in inflammation.
- A solution may provide rapid reduction in pain scores in patients without reported adverse effects or tolerance.

Theoretical Mechanisms of Action (cont’d)

- The insight that opioids exert a local analgesic effect is based on several observations:
  - Opioid receptors have been found on peripheral nerves and inflamed tissue
  - Morphine and its metabolites are largely undetectable systemically when applied topically to skin ulcers (suggesting the analgesic effect is local)
  - Peripheral opioid injections for local analgesia, such as intra-articular morphine after knee surgery, have been found to be effective in several trials


Medication Delivery Methods

- **Mouthwash**
  - Tetracaine HCl
  - Corticosteroids
  - Antifungal
  - Antiviral
  - Antifungal
  - Antimicrobial
  - Sucralfate
  - Antifoaming mouthwash base

- **Mouth gel**
  - Slow release protective coating

- **Mouthwash**
  - Medications to coat the mouth, treat pain, infections

- **Mouth gel**
  - Morphine sulfate
  - Hydromorphone HCl
  - Glycerin
  - Lemon
  - Bioadhesive slow released gel

Recent advances in novel drug delivery system. Vol. 1 No. 9 2012
www.thepharmajournal.com
Medication Delivery: Wound Gels

- Wound dressing gel
  - Aqueous gel, glycol base gel
  - Polyox bandage
- Wound dressing gels
  - Lidocaine
  - Tetracaine
  - Morphine sulfate
  - Hydromorphone HCl
  - Methadone HCl

Recent advances in novel drug delivery system. Vol. 1 No. 9 2012
www.thepharmajournal.com

Medication Delivery: Wound Gels (cont’d)

- For bed sore ulcer wounds
  - Same pain medications
  - Aloe vera
  - Phenytoin
  - Misoprostol
- Metronidazole base
- Bases
  - Intrasite gel
  - Solosite
  - Cellulose (med visc) gel
  - Propylene glycol
  - Ethoxy diglycol
  - DMAE
Medication Delivery: Topical Spray

- **Topical spray**
  - 0.1 mL per spray
  - 2 to 4 sprays to surrounding area or specific painful spots

- **Topical sprays**
  - Morphine sulfate
  - Hydromorphone HCl
  - Methadone HCl
  - Normal saline
  - Propylene glycol
  - Ethoxy diglycol
  - DMAE

Medication Delivery: Radiation Burn

- **Radiation burn gel**
  - Lidocaine
  - Tetracaine
  - Morphine
  - Hydromorphone
  - NSAID
  - Antibiotics
  - Aloe vera
  - Pluronic F127 gel (carbomer gel)
Topical Opioids Literature Review

- Literature review of topical opioids for painful cutaneous lesions
- 27 articles included, 170 patients total
- Variations in size and etiology of wounds, prep and application of topical opioids, dosage, frequency of application
- Aspects requiring monitoring: local adverse effects, systemic absorption, drug interactions

Topical Opioids Literature Review (cont’d)

- Results of review indicated that topical opioids are clinically useful and safe for controlling inflammatory pain in wounds
- Systemic absorption occurs at a safe level
- Large amount of variability amongst the available data
- Systematic approaches are required to establish effectiveness and dose-response relationship of clinical opioids to inform clinical guidelines


EBM Review of Wound Treatment

Evidence-based approach to manage persistent wound-related pain

Kevin Y Woo*, Laura K. Abbott*, and Lawrence Librach†

Purpose of review
Pain is a significant concern in people with chronic wounds. A systematised approach is recommended for the management of wound-associated pain with the objectives to address pain relief, improve function, and restore overall quality of life.

Recent findings
Combination of pharmacological agents are often recommended based on varying degree of pain severity, constenting nociceptive and neuropathic pain, and chronic inflammation related to wound associated pain. Topical agents including corticosteroids, local anaesthetics and non-steroidal anti-inflammatory drugs (NSAIDs), capsaicin, ketamine, and lidocaine/prilocaine provide pain relief with minimal side effects. Minimise dressing selection to minimise trauma, handle excess fluid, and prevent periwound skin damage has been chosen to reduce persistent wound pain. To avoid nociceptive hyperalgesia, it is important to address emotions, anticipation or negative expectation of discomfort.

Summary
Pain is a complex biopsychosocial phenomenon that requires multiple pharmacological and nonpharmacological management approach.

Keywords
nociception, pain management, persistent wound-related pain

Total Pain Assessment

Table 4. UPPER and LOWER wound infection checklist.

<table>
<thead>
<tr>
<th>Clinical evaluation of wound infection</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UPPER</strong></td>
<td>Signs and symptoms related to bacterial colonization due to infection damage in the upper wound compartment</td>
</tr>
<tr>
<td>U - unhealthy tissue</td>
<td>Presence of &gt;50% of debris, red friable tissue or abnormal discoloration of granulation tissue</td>
</tr>
<tr>
<td>P - poor healing</td>
<td>Changes in wound size of less than 10% in last 7 days</td>
</tr>
<tr>
<td>E - exudate</td>
<td>Moderate to heavy amount of exudate</td>
</tr>
<tr>
<td>R - raw</td>
<td>Presence of foul odor</td>
</tr>
<tr>
<td><strong>LOWER</strong></td>
<td>Signs and symptoms of wound infection related to bacterial damage in the lower or deeper wound compartment</td>
</tr>
<tr>
<td>L - Larger in size</td>
<td>Increase in wound size or new areas of satellite breakdown</td>
</tr>
<tr>
<td>O - oozing tissue</td>
<td>Wound that probes to bone</td>
</tr>
<tr>
<td>W - warmth</td>
<td>Increased periwound temperature of more than 2°F compared with temperature in proximal area</td>
</tr>
<tr>
<td>R - redness</td>
<td>Redness of &gt;2 cm beyond wound margin</td>
</tr>
</tbody>
</table>

## Compound Base Considerations

<table>
<thead>
<tr>
<th>Absorbency of dressings</th>
<th>Absorbency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

- Hydrofiber® technology
- Foam Dressing
- Calcium Alginites
- Capillary Action dressings
- Hydrocolloids®
- Film dressings®
- Alginate powder
- Hydrogel
- Low adherence dressings

*These dressings may be useful in rehydrating desiccated wounds.

## Wound Assessment

**Wound management in advanced illness**

<table>
<thead>
<tr>
<th>Table 3. Strategies to protect periwound skin</th>
<th>Types</th>
<th>Description</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types</td>
<td></td>
<td>Application</td>
<td></td>
</tr>
<tr>
<td>Silicon</td>
<td></td>
<td>Apply to periwound skin</td>
<td></td>
</tr>
<tr>
<td>Zinc oxide</td>
<td></td>
<td>Apply generously to skin. No need to remove all residual prior to each application</td>
<td></td>
</tr>
<tr>
<td>Acrylates</td>
<td></td>
<td>Spray or wipe on skin sparingly</td>
<td></td>
</tr>
<tr>
<td>Hydrocolloid</td>
<td></td>
<td>Window frame the stoma to prevent recurrent stripping of skin</td>
<td></td>
</tr>
</tbody>
</table>

© Wao, 2005.
GUIDELINES FOR THE USE OF
TOPICAL MORPHINE FOR
PAINFUL SKIN ULCERS IN
PALLIATIVE CARE

NHA Foundation 2012: Use of topical morphine
Effect on Wound Healing

- Still remains controversial in published literature
- More recent publications are questioning the theory that opioids impair wound healing
  - ‘Improved healing after 4 weeks of morphine gel application’
  - ‘Area under the gel healed more quickly than usual’
- Postulated to have anti-inflammatory effect within the wound, and morphine may act as an endothelial growth promoting and angiogenic growth factor


Final Compound We Use

- Morphine 10 mg (1 mL)
- Solosite 10 gm 0.1% w/w (9 mL)
- Total: 10 mL

- Morphine 10 mg (1 mL)
- Solosite 10 gm 0.1% w/w (9 mL)
- Lidocaine 2% 300 mg (15 mL)
- Total: 25 mL
### Morphine w/w/o Lidocaine Solution

![Image of Morphine w/w/o Lidocaine Solution]

### Compound Recording Example

**Beaumont**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Units</th>
<th>Amount</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine HCl</td>
<td>gr</td>
<td>1.40</td>
<td>540a</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>mg</td>
<td>50</td>
<td>540a</td>
</tr>
</tbody>
</table>

**Compounding Instructions:**

1. Obtain 1 nL 1-mg/mL 1-mL syringe and a 1-nL 1-mL syringe needle.
2. Do not use contaminated or damaged needles.
3. Discard the 1-mL syringe from packaging and put the plunger on one of the syringes.
4. Remove the sealing cap from the 1-nL syringe and fill the syringe with air from the syringe and remove the excess from the needle. 
5. Using both syringes, draw the solution into one syringe. 
6. Using the other syringe, draw the air out of the 1-mL syringe. 
7. Using both syringes, draw the solution into one syringe. 
8. Discard the excess solution. 
9. Store in a refrigerator for dispensing.

**TOTAL QUANTITY COMPONENTS:**

- **Emergency Components:**
- **Compounding Equipment:**
- **Storage:** Refrigerated

**Expiration:**

- **Expiration:**
- **Storage:** Refrigerated

**Other:**

- **Other:**
Key Questions to Consider

Ask questions like these listed below.

- Is your staff properly trained and evaluated in nonaseptic manipulation skills, gowning technique, and compounding room use?
- Do you have systems in place for handling complaints and investigating adverse events?
- Do you purchase pharmaceutical-grade chemicals (USP, NF equivalent) from FDA-registered suppliers?
- Do you obtain Certificate of Analyses for all formula ingredients?
- Do you maintain both master formulas and lot-specific worksheets for all compounds?
- Can you immediately trace a prescription back to original formula log sheet and source of ingredients?
- Is every step of the compounding process from prescribing to compounding and labeling through dispensing reviewed and verified by a licensed pharmacist?
- Do you verify potency of finished compounds via weight, volume, and yield checks; can you share results within 48 hours?
- Are your pharmacists, technical and customer care staff dedicated to compounding?

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Patient Case

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Patient Case (cont’d)

- Colorectal excision with rectal reconstruction, rectal cancer
- Prior to topical morphine, patient required 500 mg oral morphine equivalent
- With topical morphine gel, reduced to 20 mg of oxycodone per day

Indications for Use

- Due to difficulty with medication procurement (resources needed for extemporaneous compounding), patients must be reviewed by a specialist
- The following criteria should be followed:
  - Terminal or palliative care patients only
  - Painful superficial chronic wounds (broken skin) <10 cm diameter
  - Non-neuropathic, localized pain
  - Opioid naïve patients, history of addiction to drug or alcohol—only where the introduction of systemic opioids would be inappropriate, or is refused by the individual patient
  - Opioid tolerant patients—only where the side effects prevent adequate dose escalation of the systemic opioid dose

NHA Foundation 2012: Use of topical morphine
Exclusion Criteria

- Hypersensitivity (eg, rash) to morphine or other opioid derivatives
- Children and individuals ≤18 years of age
  - Do not use in or around the eyes because the products are not suitable for such applications
  - Do not use in wounds with excessive exudate or bleeding because the gel will not adhere to the wound surface
    - Topical morphine causes vasodilation leading to more bleeding
  - Acute respiratory depression
  - Topical management of infected wounds—systemic treatment should be considered

NHA Foundation 2012: Use of topical morphine

Administration

- Apply entire contents of syringe **topically** to each wound with each dressing change, up to a maximum of 3 times per day
- Nurse must use gloved hand to evenly distribute medication throughout entire wound
- Nurse to dispose of glove and topical syringe in the sharps container (in compliance with controlled substance disposal policy)
- Do NOT apply external heat to wound
- Apply ordered dressings to wound following medication application
- Patient to avoid showering, bathing, or washing application sites for at least 1 hour
Adverse Effects

- Monitoring is the same as systemic opioids
  - Excess sedation
  - Respiratory depression
  - Pruritus
- Drug interactions: CNS depressants, opioid agonists, sedatives, and hypnotics (additive respiratory and CNS depressive effects)

Cautions

- Intolerance to systemic side effects of morphine or other opioid derivatives
- Severe renal impairment (eGFR <30ml/min) or severe hepatic impairment
  - Used in preference to systemic treatments for this very reason
- Severe impairment of central nervous system (head injury or raised intracranial pressure)
  - Used in preference to systemic opioids to reduce the risks of side effects
- Monitor carefully for signs of opioid accumulation and toxicity over time
- Care in bleeding or exuding wounds due to reduced inability of the Intrasite® gel or chosen base to adhere to wound surface
  - Morphine has vasodilatory effect and may increase bleeding if hemostatis not achieved
- Hydrogels have a propensity to macerate if left on too long or if an excessive amount of the gel is applied

NHA Foundation 2012: Use of topical morphine
Adverse Effects

- Very few side effects have been reported within the literature available regarding the use of transdermal morphine
- There is a potential for systemic absorption especially over large areas or with higher concentrations
- Patients should be monitored closely for opioid side effects, especially if taking systemic opioids concomitantly
- Pruritus, burning, and discomfort at site of application of morphine gel has been reported when using Intrasite/Solosite gel®, which contains propylene glycol
  - Add lidocaine to reduce burning discomfort or change base
- Propylene glycol has been reported to be a potential irritant and sensitizing agent in a small number of patients

NHA Foundation 2012: Use of topical morphine

Challenges/Future Concerns

- Expanding use of topical opioid by other services (wound care, plastic surgery)
- Inpatient and outpatient pharmacy keeping up with patient/service demand—need to outsource compounding
- When patient discharged (home or LTAC), will their insurance cover the topical opioid, and who will supply compounded medication?
References


References (cont’d)