Creams, Gels and Magic Spells

The use of topical agents in acute and chronic pain

Conflict of Interest Disclosure

- Author’s conflict of interest
  - Teva Pharmaceuticals: Speaker Bureau
  - Innovo Pharmaceuticals: Speaker Bureau

Objectives

- Review the historical use of topical agents for pain control
- Compare the pros and cons of topical analgesia
- Understand the mechanism of action of topical agents on the peripheral mediators of pain
- Summarize the available FDA approved formulations of current topical pain modalities and their indications
- To explore the use of compounded agents, their mechanism of action and the evidence supporting their use
- Identify appropriate candidates for topical analgesics through the use of case studies
The history of topical agents

- Egyptians
- Ancient Greece
- Native Americans
- Chinese Medicine
- Reader’s Digest

Why does this presentation matter?

- Topical agents offer one more modality to use in our tool box of pain fighting weapons
- The body of evidence supporting the use of topical agents is growing... it is more than just hocus pocus or a placebo effect
- If we don’t believe in it, why would our patients believe in it?

Pros of topical analgesia

- Ease of use
- Lack of stigma
- Low incidence GI or CNS side effects
  - Topical NSAIDs have a decrease incidence of cardiac and GI side effects compared to oral NSAIDs
- Minimal drug interactions as there is minimal systemic absorption
- Safety
- Option for when the oral route is not desirable
- Cost (when treatment of side effects is considered in overall treatment costs)
- Efficacy
  - Evidence in multiple disease states
  - OA, epicondylitis, muscle strain, post-herpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN)

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Cons of topical agents

• Application site irritation: most common side effect is pruritis/dryness (approx 10%)
• Mobility limitations of the patient may make application to the affected area difficult
• Variations in absorption due to variations in skin thickness
• Cost: if using outside of the approved labeling or if the patient is uninsured


Be creative to get around the obstacles!

The mechanism of action of topical agents on the peripheral mediators of pain
Excitatory mechanisms

- Substance P: Generates greater postsynaptic response and enhances the activity of NMDA receptors
- Histamine
- Glutamate
  - Excitatory amino acid
    - Continued stimulation causes expression of a second glutamate-responsive receptor, NMDA
- Prostaglandins
  - More of a sensitizing agent than an activating agent; sensitizes neurons to bradykinin
- Tumor Necrosis Factor
  - Pro-inflammatory
- Nerve Growth Factor
  - Regulates the expression of the neuropeptides (substance P and CGRP) and receptors (NK1 and Bradykinin 2) and the ion channels
- Interleukins
  - Stimulates the proliferation of T cells
- Bradykinin:
  - Vasodilator; increases capillary permeability; stimulates pain receptors
**Transduction**

- Sodium is used for action potential
  - channels closed at rest and opened at activation
  - can be blocked by local anesthetics such as lidocaine
- Calcium mechanism is similar
  - Can be affected by anticonvulsants such as gabapentin


**Transmission**

- Transduction initiates an action potential to transmit the signal to the CNS
- The A delta and C Fibers release excitatory neurotransmitters including glutamate which binds to NMDA receptors to promote pain transmission.
- By interrupting any aspect of this cascade, the pain response can decrease

Persistant Neuropathic Pain (versus acute injury)

- Normal transduction/transmission is mediated by ion channels
- Mechanisms of persistant pain:
  - Hyper-excitability: Nerve endings in the periphery are damaged by noxious stimuli and nearby keratinocytes may be factors in abnormal re-organization of the nervous system
  - Increased expression of sodium channels
- Sympathetically mediated pain
  - Sympathetic neurons sprout into the dorsal root ganglia of the injured sensory neurons and post-injury sympathetic neurons sprout into the dermis
- Peripheral sensitization
  - Sensitized nociceptors have a lowered threshold for activation and an increased rate of firing
  - Generate nerve impulses more readily and more often

1. Gilron I, Watson PN, Cahill CM, Moulin DE. Neuropathic Pain: A Practical Guide for the Clinician. CMAJ 2006; 175(3); 265-2

Current available FDA approved formulations of topical agents

- Patch 5% (Lidoderm): PHN
- Gel 5% (lidocream): anorectal pain
- Ointment 2.5%/2.5% lidocaine/prilocaine (EMLA)
- Cream 7%/7% lidocaine/tetracaine (Pliaglis)

- Evidence for use
  - PHN study: 65% improvement of pain and 77% improvement of quality of life at week one, at completion (4 weeks) 58% of pt had moderate to complete relief of pain
  - Pharmacokinetic study of patch: plasma concentration with topical lidocaine 8x lower than concentration needed for anti-arrhythmic effects and 25x lower than concentration for toxicity
  - SAFE! 3± 2% of lidocaine is absorbed systemically

2. Gilron I, Watson PN, Cahill CM, Moulin DE. Neuropathic Pain: A Practical Guide for the Clinician. CMAJ 2006; 175(3); 265-2
**Diclofenac**

- **Mechanism of action:**
  - blocks the prostaglandin pathway
- **Available forms:**
  - Gel 2% (Pennsaid): OA of the Knee
  - Patch 1.3% (Flector): acute pain due to minor strains, sprains, and contusions
  - Gel 1% (Voltaren): joint pain of osteoarthritis in the knees, ankles, feet, elbows, wrists, and hands

**Capsaicin**

- **Mechanism of action:**
  - Binds to TRPV1 (a heat activated calcium channel)
  - Prolonged activation of these neurons depletes presynaptic substance-P
- **Available Forms:**
  - OTC preparations (Capsagel, Salonpas-Hot, Zostrix)
  - Patch 8% (Qutenza): Approved for use in PHN but requires pre-treatment with local anesthetic
- **Studies have shown efficacy in**
  - painful HIV-associated neuropathy
  - treatment of intermetatarsal neuroma (Morton’s Neuroma)
  - Postherpetic neuralgia
  - Erythromelalgia

**Clonidine gel**

- **Mechanism of Action:**
  - Alpha 2 agonist, effects the norepinephrine blockade, increases GABA activity
- **Although an FDA approved drug, use in pain is off-label.**
- **Evidence supporting use in diabetic neuropathy**
Compounded Agents

Are they safe? Are they worth it?

What are compounding pharmacies?

- Make drugs prescribed by doctors for specific patients with needs that cannot be met by commercially available drugs
- Make approximately 3% of drugs dispensed in the U.S.
- Approximately 7500 nation-wide specialize in "advanced compounding services" with less than ½ of those providing sterile products

Are they safe?

- The FDA regulates drug manufacturers, states regulate pharmacies.
- State boards of pharmacy: ensure that pharmacies follow state regulations for pharmacy practice.
- FDA regulates the active pharmaceutical ingredients used in the compounded medications
- DEA regulates the compounding pharmacies’ handling of controlled substances.
- Is it PCAB accredited? Currently held by 180 pharmacies.

What's in the Magic mixture?

NSAIDS

1. Efficacy and safety of all topical NSAIDs reviewed in chronic and acute pain conditions,
   - incidence of systemic adverse events were low and the adverse effects were no different than placebo
   - Effective in relieving pain
2. Studies in multiple pain conditions
   - Lateral epicondylitis (diclofenac)
   - Knee pain (ibuprofen)
   - Tendonitis (ketoprofen)
   - Sports induced muscle strain (ketoprofen vs diclofenac)

Options

- Lidocaine
  - nerve conduction blockade through Na channel blockade
- Bupivacaine
  - nerve conduction blockade through Na channel blockade
- Baclofen
  - GABA agonist
- Ketamine
  - NMDA blockade
  - studies in PHN, CRPS, lumbar radicular pain, chemo-induced neuropathy

More options

- Capsaicin
  - acts on Substance P
  - studies in PHN and diabetic neuropathy

- Diclofenac
  - COX inhibitor
  - studies in epicondylitis, tendonitis, OA, muscle strains

- Cyclobenzaprine
  - inhibits presynaptic uptake of NE

- Dextromethorphan
  - NMDA receptor blocker

1. Gilron I, Watson PN, Cahill CM, Moulin DE. Neuropathic Pain: A Practical Guide for the Clinician. CMAJ 2006; 175(3); 265-2

Yup, still more options

- Gabapentin
  - Glutamate antagonist, regulates Na and Ca channels

- Carbamazepine
  - NMDA and Na Channel Blocker

- Clonidine
  - Alpha 2 Agonist, NE blockade, Increase GABA activity

- Amitriptyline
  - inhibits presynaptic uptake of NE and 5HT. Na and Ca Channel blockade, NMDA blockade

- Pentoxifylline
  - TNFa inhibitor

CRPS

Bob is a 44 year old disabled UPS worker. Status post multiple failed back surgeries.

- Current medications:
  - high dose opioids, oral anticonvulsants, oral muscle relaxants. Cannot take oral anti-inflammatories due to GI issues.

- Interventional therapies:
  - Has a spinal cord stimulator. Short term improvement with lumbar intra-articular facet injections

- Symptoms:
  - severe radicular pain and profound hypersensitivity over his low back area

- Family history:
  - mother with CRPS
CRPS treatment plan

- Ketamine 10%
- Gabapentin 10%
- Diclofenac 5%
- Cyclobenzaprine 3%
- Bupivcaine 2%
- Baclofen 5%
- Clonidine 0.5%

Results
- Did not help his leg pain
- Did help with the sensitivity of his low back
- This allowed him to sit back against a chair

Osteoarthritis

Joe is a 59 year old heavy machine operator with severe osteoarthritis of his finger.

Interventions:
- tried and failed intra-articular injections
- Cannot move forward with corrective surgery, i.e. fusion of the joint
  - cannot lose mobility of the hand and maintain his job

Current medications:
- good relief with oxycodone-acetaminophen (percocet) at night but cannot take opioids while on the job
- reported only mild relief with diclofenac 1% gel

OA treatment plan

- Ketamine 10%
- Gabapentin 10%
- Diclofenac 5%
- Cyclobenzaprine 5%
- Lidocaine 10%
- Pentoxifylline 5%

Results
- Patient was able to use it multiple times through the day
- Remained at work
- Maintained his opioids at a low level
Chemo-induced neuropathy

Kimberley is a 24 year old female with a history of gestational trophoblastic disease treated with chemotherapy at age 18

- Symptoms:
  - Complaints of deep aching hypersensitivity of her lower extremities
- Interventional:
  - Not a candidate for nerve blocks
  - Some relief with a TENS unit
  - Afraid of trying a spinal cord stimulator
- Current medications:
  - Long and short-acting tapentadol (Nucynta)
  - Tried and failed multiple opioids including a fentanyl patch, methadone, oxycodone products, dilaudid
  - Tried adjuvent medications including lypica and gabapentin

Chemo-neuropathy treatment plan

- Ketamine 10%
- Gabapentin 10%
- Diclofenac 5%
- Cyclobenzaprine 5%
- Bupivacaine 2.5%
- Baclofen 3%
- Pentoxifylline 3%

- Pt reported improved stamina for aggravating activities, ie: standing and walking any distance
- Pt was able to discontinue her long acting tapentadol (Nucynta ER)

Other appropriate patient types

Acute Pain
- Sprains
- Rib Fractures
- Epicondylitis

Chronic Pain
- Post mastectomy
- Post herpetic neuralgia
- Fibromyalgia
- Pudendal neuritis
The moral of the story....

- Topical options are a comparatively safe, effective option for the patient suffering with pain.
- There is research supporting the use of topical agents in a variety of pain states although more research is needed.
- It’s time to think outside the box in an effort to utilize every modality we can that potentially help the patient.
- That’s how we got here, right?

References