Stick it to me:
Topical and transdermal analgesics
at end of life

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Learning Objectives
• Describe the evidence regarding efficacy and
toxicity of topical analgesics, and proposed
roles in caring for patients with advanced
illness.
• Describe patient- and agent-related variables
that affect the selection and use of
transdermal opioids (e.g., fentanyl and
buprenorphine), including equianalgesic
conversions and timing considerations when
switching to and from a transdermal opioid.

Transdermal vs. Topical Analgesics
• “Transdermal” analgesics
  – Fentanyl
  – Buprenorphine
  – Predominantly central (systemic) effects
• “Topical” analgesics
  – Applied to skin at site of pain
  – Predominantly a peripheral effect

So... What About Lidoderm?
5% Lidocaine Patch (Lidoderm)

- Indicated for treatment of post-herpetic neuralgia
- Topical preparation
- In patients with normal hepatic function, blood levels of the drug are minimal
  - On 12 hours, off 12 hours (max 3 patches)
  - Adequate trial is 2 weeks
- Only adverse effect is mild skin reactions (erythema or rash)

Davies PS, Galer BS. Drugs 2004;64(9):937-947.

Cochrane Review

- May benefit some patients on an individual basis.
- Two studies showed improvement vs. placebo.
- There is stronger evidence for the use of other drugs.
- Side effects minimal; include irritation and redness.
- Unable to recommend as first line for PHN.

What else can we use it for?


Pharmacokinetics and safety of continuously applied lidocaine patches 5%

- Randomized, prospective, multiple-dose, open-label pharmacokinetic study
- Ten subjects – four lidocaine patches every 24 hours (group 1)
- Ten subjects – four lidocaine patches every 12 hours (group 2)
- Serum samples of blood drawn to assess skin data and overall tolerability and safety were assessed with skin sensory testing

Pharmacokinetics and safety of continuously applied lidocaine patches 5%

- Mean steady-state Cmax values:
  - Group 1 (every 24 hours) = 186 ng/ml
  - Group 2 (every 12 hours) = 225 ng/ml
- 1/7 that of antiarrhythmic effect (~1500 ng/ml)
- 1/25 that at which toxicity increases (~5000 ng/ml)
- No sensory alterations at patch administration site

Capsaicin

- The component of chili peppers that makes them HOT
  - Acts primarily as a counterirritant
  - Activates nerve fibers in the skin, which becomes desensitized over time as a result of depletion of substance P and calcitonin gene-related peptides
  - Desensitization due to reversible nerve degeneration
  - After therapy discontinued, epidermal nerve fibers are reinnervated over a 6 week period.

Capsaicin Efficacy

- 12 week double-blind trial
- 113 patients with mild-to-moderate OA pain (primarily of the knee) randomized to:
  - Capsaicin 0.025% cream vs Vehicle cream QID
- Results: Capsaicin superior to vehicle, but not until week 4
- Conclusion: capsaicin provided modest analgesia in some patients with relatively mild baseline pain, but analgesia was neither rapid nor sustained and patients frequently self-medicated to maintain adequate pain relief

Capsaicin Safety

- Not associated with serious adverse events, but accidental contact with the eyes or mucus membranes is extremely irritating
- Adverse event rate = 54%
  - Placebo adverse event rate = 15%
- Wash hands immediately after use
- Use of lidocaine jelly?

Non-oral diclofenac preparations available in U.S.

- Diclofenac epolamine 1.3% topical patch (Flector®)
- Diclofenac sodium 1.5% topical solution (Pennsaid®)
- Diclofenac sodium 1% topical gel (Voltaren® Gel)
- Diclofenac sodium 3% topical gel (Solaraze® Gel)

Note: diclofenac epolamine 1.3% topical patch and diclofenac sodium 3% topical gel are not FDA approved for use in chronic musculoskeletal pain.
Diclofenac Adverse Effects

- Cardiovascular risk – boxed warning
  - Perioperative use in CABG contraindicated
  - May cause increased risk of MI and stroke, which can be fatal
  - Risk may be greater with longer duration and pre-existing CV disease
- Gastrointestinal risk – boxed warning
  - Increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation.
  - Events may occur at any time during use and be asymptomatic
- Elevated liver transaminases

Diclofenac 1% Gel (Voltaren® Gel)

- Indicated for the relief of the pain of OA of joints amenable to topic treatment
- Dosing – do not exceed 32 grams each 24hrs
  - Lower extremities – 2 grams QID
  - Upper extremities – 4 grams QID
- Avoid exposing application site to:
  - Sunlight or similar
  - Direct heat
  - Sunscreens, moisturizers, insect repellants, etc.

Diclofenac gel (Voltaren® Gel) in OA of the knee


Diclofenac sodium topical solution 1.5% (Pennsaid®)

- Indicated for the treatment of signs and symptoms of osteoarthritis of the knee
- Dosing
  - 40 drops to affected knee QID
  - Dispense only 10 drops at once
- Avoid showering / bathing for 30 minutes
- Avoid exposing application site to:
  - Sunlight or similar
  - External heat or occlusive dressings

Comparative Cmax of diclofenac


Application of Voltaren 1% Gel

Voltaren 1% Gel Prescribing Information

Diclofenac gel (Voltaren® Gel)
Voltaren 1% Gel 3/5 Pack

- Three 100 g tubes = $82.98
- Five 100 g tubes = $138.30

www.drugstore.com

Diclofenac / DMSO (Pennsaid®) solution in OA of the knee


T-Diclo: topical diclofenac; O-Diclo: oral diclofenac; DMSO: dimethyl sulfoxide

Adverse Effects


Questions Unanswered

- Can topical diclofenac be safely administered to:
  - those with cardiovascular disease?
  - those with history of peptic ulcer disease?
  - those with history of NSAID associated upper gastrointestinal bleeding?
  - those on concurrent anti-platelet or anti-coagulation therapy?

  NO DATA!

Salicylates

- Mechanism of action – counterirritant
  - May interfere with transcription factors and kinases involved in inflammatory processes
  - Do not appear to work through COX inhibition
    - 100 fold less potent than COX-2 inhibitors
  - Trolamine salicylate – undetectable in serum
  - Methyl salicylate applied for four days
    - BenGay, Icy Hot
    - Achieved a low systemic serum concentration
  - Efficacy – poor in chronic pain states

Altman R, Barkin RL. Postgraduate Medicine 2009;121:139-147.

Salicylates

- Safety
  - Methyl salicylate has been associated with severe toxicity and deaths after topical application or with accidental or deliberate ingestion
  - Methyl salicylate potentiates effects of warfarin, increasing bleeding risk
  - Adverse side effects more similar to oral NSAIDs compared to other topical products
    - Must consider safety profile when using in patients (decision to avoid ORAL NSAIDs is a reason to avoid using topical salicylates)
Compounded Opioids for Wound Care

- MOA: act on peripheral opioid receptors that are expressed in inflamed tissues
- Dose:
  - 10 mg of IV morphine sulfate + 8 grams of intrasite gel (compound pharmacy)
  - Apply to wound 1-3 times daily
- Side effects: site irritation (e.g. itching, burning, redness)
- Limited systemic absorption

Topical Opioids

- There is conflicting data regarding the efficacy of topical opioids (morphine) in the treatment of ulcers compared to placebo.
  - Recent trials published in 2009 and 2011 did not find statistically significant data regarding the use of topical morphine
  - However, numerous other studies and case reports have shown the efficacy of topical morphine for wound pain reduction
- Conclusion:
  - Although there exist contradictory data, topical morphine can be an effective alternative to treat patients with wound pain in palliative care
  - Safe with very little to no systemic absorption

Topical Opioids in Palliative Care

- Review of literature concludes:
  - There is support for the use of topical opioids
  - No clear direction to make clinical recommendations regarding
    - Ideal opioid
    - Starting dose
    - Interval of administration
    - Methods of titration
    - Carrier

Fentanyl

- Synthetic pure mu opioid agonist
- 75-100 times more potent than morphine (mg-to-mg basis)
- Greater lipid solubility than morphine
  - Facilitates rapid diffusion across the BBB
  - Quick onset of action
- Parenteral – IV injection, IV infusion, SQ infusion, IM injection (no, no, bad dog), TD, TM

Transdermal Fentanyl

- Apply every three days for stable chronic pain
- Low MW and high solubility in both fat and water, therefore good candidate for TD administration.
  - 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h
- Gel-containing reservoir, drug-in-adhesive matrix, matrix membrane patch

Variables that affect absorption

- Area of application / hair
- Increased body temperature
- Cachexia / low body weight patients
  - Poor fat stores, debilitated patients, muscle wasting and altered clearance
- After TDF removal, about half the drug has been eliminated after 17 hours

Indications

- Management of persistent, moderate to severe chronic pain in opioid-tolerant patients 2 years of age or older who require a total daily dose of opioid at least equivalent to TDF 25 mcg/h:
  - Oral morphine 60 mg/d for ≥ 1 week
  - Oral oxycodone 30 mg/d for ≥ 1 week
  - Oral hydromorphone 8 mg/d for ≥ 1 week
  - Oral oxymorphone 25 mg for ≥ 1 weeks
- Contraindicated in post-operative pain, mild pain, intermittent pain
- Caution with 3A4 inhibitors

Conversion to TDF

Fentanyl Tidbits

- Converting from oral LA opioid to TDF
  - If patient not taking oral morphine, convert to oral morphine
  - Using the 2 mg oral morphine/day ~ 1 mcg/h TDF, calculate TDF patch strength
  - Advise patient to take one last dose of the oral long-acting opioid at the same time the first TDF patch is applied
  - Increase TDF if necessary in 3 days, and every 6 days thereafter

Fentanyl Tidbits

- Converting from ATC SA opioid to TDF
  - If patient not taking oral morphine, convert to oral morphine
  - Using the 2 mg oral morphine/day ~ 1 mcg/h TDF, calculate TDF patch strength
  - Advise patient to take two or three scheduled doses of their oral SA opioid after TDF patch application: one at the time of patch application, another 4 hours later, and another 4 hours later if needed
  - Increase TDF in 3 days if necessary, then every 6

Fentanyl Tidbits

- Titrating TDF upward
  - After initiation of TDF therapy, evaluate use of rescue opioid on days 2 and 3. If patient using > doses of rescue opioid, calculate TDD of rescue opioid and increase TDF patch in equivalent amount
  - Increase by 25-50 mcg/h, but not to exceed a 100% increase. No dosage increase should exceed 50 mcg/h
    - Increase from 25 to 50 mcg/h
    - For patients on ≥ 50 mcg/h, increase by 50 mcg/h
**Fentanyl Tidbits**

- Converting from TDF to an oral opioid
  - Based on the TDF patch strength, calculate oral morphine equivalent (2 mg oral morphine/day = 1 mcg/h TDF)
  - Once the new opioid product is in the patient’s home, remove TDF patch
  - For the first 12 hours after patch removal, use only the previously prescribed rescue opioid
  - 12 hours after patch removal begin with 50% calculated scheduled opioid regimen; rescue available
  - 24 hours after patch removal, increase to 100% calculated opioid regimen; rescue available

- Converting from TDF to IV fentanyl
  - Establish IV access, remove TDF patch
  - Allow “as needed” bolus dose of fentanyl
  - Six hours after TDF patch removal, begin 50% of IV fentanyl infusion (which should be 50% of the patch strength); bolus option remains in place
  - Twelve hours after TDF patch removal, increase IV fentanyl infusion to 100% of prescribed amount (which should be equal to the TDF patch strength); bolus option remains in place

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**Butrans (BU-tranz)**

- Transdermal buprenorphine indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time
  - Osteoarthritis, low back pain
- Available as 5 mcg/h, 10 mcg/h, 20 mcg/h
- Schedule III

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**Butrans**

- Each patch is meant to be worn for 7 days
- Apply to upper outer arm, upper chest, upper back or the side of the chest. Do not re-use site for 21 days.
- In opioid-naïve patients the initial dose should always be 5 mcg/h
- Converting to Butrans:

  - The oral morphine : transdermal buprenorphine equipotency ratio is between 1:70 and 1:100 (1:75 most commonly published).
  - mg buprenorphine/day x 75 = mg oral morphine/day
  - For example, consider the Butrans 10 mcg/hour patch:
    - \( \frac{[buprenorphine \text{ 10 mcg}]}{[24 \text{ hr}]} \times \frac{[1 \text{ mg}]}{[1000 \text{ mcg}]} = \frac{[0.24 \text{ mcg buprenorphine}]}{[75 \text{ mg}]} = 18 \text{ mg oral morphine/day} \)
Butrans
• Mercadente et al determined ratio is 1:70


Butrans (BU-tranz)
• Advantages over TDF:
  – Lower abuse potential
  – Less dangerous in an overdose
  – Causes fewer withdrawal symptoms
• Contraindications and Precautions
  – Significant respiratory depression, asthma, paralytic ileus
  – Acute post-op, mild, or intermittent pain
• Cost for 4 patches (1 month) AWP
  – 5 mcg/hour - $151.20
  – 10 mcg/hour - $226.80
  – 20 mcg/hour - $401.52

Mrs AG
• 81 yo AAF with progressive dementia. She was admitted because of a mental status change at ALF, medical team suspected aspiration pneumonia however found lung mass c/w cancer
• PMH: ESRD on HD, OA, COPD, CAD
• Meds PTA included percocet 5/325 for arthritic pain but daughters could not quantify use
• Family: four daughters all involved in her care

Mrs AG
• PE: cachectic, appears sedated and unresponsive, two stage II ulcers
• Pain Regimen: Hydromorphone 1mg IV q2hours (receiving 5/day)
• Consultation requested and family meeting held to discuss options
  – Daughters recognize decline of pt and have realistic expectations considering likely cancer dx
  – Primary family concern was sedation and pain

Mrs AG
• 5 mg IV HM= 100 oral morphine= 50 mcg/hr fentanyl patch
• Individualize dose:
  – decrease by 25-50% sedation and cross tolerance
• Start Fentanyl 25 mcg/hr TD q72 hours

Is that all?
Mrs AG

Orders:
- Start Fentanyl patch 25 mcg/hr TD q72 hours - place now (9 am)
- Give oxyfast (oxycodone concentrate 20 mg/ml) 10 mg buccally q4 hours standing x3 doses then change to q2h prn
- Next day patient appeared much more comfortable to our team, staff and family
- Discharged to NH with palliative plan (no hospital transfer) with family agreement

Mrs AG...

One Month Later

- She is admitted from NH after a fall leading to a hip fx. She is s/p hip repair and spent one week in ICU requiring ventilator support post-op. We are consulted and meet with family because she is not weaning off ventilator.
  - Primary concern: “we think she is suffering, can’t you do something about the pain?”

Mrs AG

Pain Regimen: Fentanyl 75 mcg/hr TD q72 hours
- At NH increased from 25 mcg/hr patch to 50 mcg/hr patch after one week
- Two weeks later increased to 75 mcg/hr

Mrs AG

Team is concerned that she may not wean off the vent (trach or w/d?) and also noting pain
- IV fentanyl drip and boluses

Considerations
- TD → IV conversion
- Given titration in cachectic patient, how much credit do we give the current patches?

Mrs AG

Go back to what you last knew... TDF 25 mcg/hr patch worked and well tolerated
- 25 mcg/hr patch = 25 mcg/hr IV fentanyl
- Started a 25 mcg/hr fentanyl drip with 25 mcg IV q1hr prn (D/C’d patch)
- At 6 hours, start continuous infusion at 12 mcg/h; at 12 hours increase to 25 mcg/h; keep bolus
- She did not require further titration and after next family meeting, a terminal ventilator withdrawal was scheduled for the next day.