DISCLAIMER I

Compounding pharmacist and owner of

Lloyd Center Compounding Pharmacy

and

Pacific Compounds Pharmacy
DISCLAIMER II: I LIKE CATS.

Pain is nature's way of saying "Don't do that."

Painkillers are mankind's way of saying "Just watch me."
OBJECTIVES

• Understand which agents can be compounded to provide wound healing and reduce scarring

• Analyze effectiveness and mechanism of each medication in wound healing

• Develop plan for prescribing topical wound healing compound combinations
BASES USED IN WOUND CARE
LIPOSOMAL BASES

- Liposomes allow enhanced penetration through skin even for hydrophilic drugs

- Elastic liposomal vesicles are able to fit between stratum corneum cells to deliver drug intact to deeper tissues

- Effect is comparable to subcutaneous injection
PRACAXI OIL BASE

• Traditionally, pracaxi oil used to treat snake bites, ulcers, stretch marks and infections

• High in fatty acids – improves wound healing and enhances drug delivery

• Mixed into a silicone base
  • Silicone gel sheeting used in scar treatment and prevention
  • Easier to use than sheets

Fig. 2 Surgical scar 10 days after osteochondral allograft surgery a before and b 2 weeks after application of compounded base containing pracaxi oil.

Fig. 4 Radiation burn to the right side of the head and neck a before and b 2 weeks after application of compounded base containing pracaxi oil.

Fig. 8 Traumatic injury to the left (a) and right (b) elbows before and to the left (c) and right (d) elbows 11 days after application of a compounded medicine comprising 2% mupirocin in a topical anhydrous silicone base containing pracaxi oil; the injuries to the left (c) and right (d) elbows were much improved.

Fig. 6 A second degree facial burn on the face of a 5-month-old infant a before and b 8 days after application of compounded base containing pracaxi oil.
**OINTMENTS & GELS**

- Can also use inert, hypoallergenic bases
  - Ointments provide protective barriers
  - Commonly white petrolatum

- Some studies have used zinc oxide ointments

- Negative: can be difficult to wash out of wound
  - Can use water-based gels for deep wounds
    - Pluronic gel has unique properties

You gots a lil something there
AGENTS TO ACCELERATE WOUND HEALING
PHENYTOIN

- Traditionally used as anticonvulsant: adverse effect of gingival hyperplasia used to our advantage

- Multiple additional effects
  - Collagen deposition
  - Proliferation of fibroblasts
  - Granulation tissue formation
  - Neovascularization
  - Inhibition of collagenase
  - Also shown to reduce bacterial contamination

PHENYTOIN

- 40 leprosy patients with chronic trophic or plantar ulcers were given phenytoin in zinc oxide paste
  - 82.5% had granulation formulation
  - 55% had complete resolution

- 100 diabetic patients with grade I/II foot ulcers
  - Decreased wound slough and discharge
    - Day 14 only 22% vs 84% of control saline
  - Faster formation of granulation tissue
  - Shortened hospital stay

SUCRALFATE

- Forms protective mechanical barrier by binding to mucosal proteins

- Cytoprotective – promotes prostaglandin E$_2$ and nitric oxide synthesis locally
  - Increases blood flow and mucus production

- Stimulates granulation tissue formation

- Evidence of antibacterial activity

Gupta et al Dis Colon Rectum 2011
SUCRALFATE

• Second degree burn study in rats showed better efficacy than silver sulfadiazine 1% cream

• 22 patients with rectal bleeding post-radiotherapy
  • 73% clinical improvement with complete resolution in 32%

• 76 patients with wounds from low anal fistulotomy
  • Higher mucosal coverage and complete wound resolution
  • Lower postoperative pain

<table>
<thead>
<tr>
<th>Postoperative week</th>
<th>Placebo (n = 37)</th>
<th>Sucralfate (n = 39)</th>
<th>P</th>
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<tbody>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>.12</td>
</tr>
<tr>
<td>4</td>
<td>2 (5)</td>
<td>11 (28)</td>
<td>.008</td>
</tr>
<tr>
<td>6</td>
<td>27 (73)</td>
<td>37 (95)</td>
<td>.009</td>
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</table>

Data are numbers of patients with percentages in parentheses. NS = not significant.
**FIGURE 2.** Effect of sucralfate ointment compared with placebo on postoperative pain in patients after low anal fistulotomy. VAS = visual analog scale (0 = no pain; 10 = very severe pain). *P < .02; **P < .01.
ASCORBIC ACID

- Antioxidant
- Cofactor for collagen synthesis
- Promotes fibroblast migration
- Encourages matrix deposition
- Causes neovascularization

Mohammed et al Int Wound J 2015
ASCORBIC ACID

• Ascorbic acid levels drop 60-70% at wound site

• In knockout mice with low plasma levels:
  • ↓ healing rate
  • ↓ wound healing modulator production
  • ↑ pro-inflammatory cytokines

• Topical application of honey and oral consumption of ascorbic acid healed venous ulcers in 18 patients

ASCORBIC ACID

Day 7

A: Sufficient
B: Deficient
C: Deficient + AscA

Day 14

D
E
F

Mohammed et al Int Wound J 2015
MISOPROSTOL

• Synthetic prostaglandin E₁ analog with cytoprotective properties

• Used in gastric and decubitus ulcers and radiation burns

• Limited literature – decreased healing time of acute surgical wound in rats
  • May be more effective in acute wounds vs. chronic

Mahoney et al Wounds 2007
### SUMMARY WITH DOSAGES

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>1-5%</td>
</tr>
<tr>
<td>Sucralfate (Carafate)</td>
<td>7-20%</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>1-2%</td>
</tr>
<tr>
<td>Misoprostol (Cytotec)</td>
<td>0.0024%</td>
</tr>
</tbody>
</table>
Touch me like that again, buddy, and I'll teach you the meaning of "nevermore"
AGENTS THAT ALSO PREVENT SCARRING
SCAR PREVENTION

• Scar prevention is a key part of wound healing
  • Atrophic, striae, contracture, hypertrophic, keloid

• Add these agents into wound care formulations
  • Critical for scar prevention to improve elasticity
  • Keloid or hypertrophic scars are incredibly difficult to treat so prevention is key

• Can take months to years to treat existing scars
BETA GLUCAN

• Immunomodulator
  • Stimulates fibroblasts to encourage collagen deposition
  • Improves wound tensile strength
  • Increases tissue granulation

• Retrospective review of 43 pediatric burn cases
  • 79% of cases reduced analgesic requirements, need for dressing changes and improved cosmetic appearance

• Showed anti-oxidant properties in burn-induced tissue damage in rats

DIMETHYL SULFONE (MSM)

- Natural organosulfur compound with antioxidant and anti-inflammatory properties
- Mechanism not well understood
- Down-regulates expression of interleukin-6 and interleukin-8
- Modulates apoptosis caused by excessive nitric oxide production

Kloesch et al Life Sci 2011, Karabay et al Immunopharmacol Immunotoxicol 2014
ALOE

- 75 potentially active components – 6 are antiseptic
- Wound healing, antioxidant, immunomodulatory effects
- 50 patients with second degree burns
  - Aloe vera gel vs. silver sulfadiazine 1% cream BID
- Patients receiving aloe had faster pain relief, higher rate of wound healing, fewer hypertrophic scars

Shahzad and Ahmed J Pak Med Assoc 2013
EGCG: EPIGALLOCATECHIN-3-GALLATE

• Green tea polyphenols – catechins

• Antioxidant, anti-inflammatory and protective properties in skin

• EGCG alters
  • Collagen production
  • Collagenase activity
  • Transforming growth factor (TGF) β1 actions

EGCG

- Induces keratinocyte differentiation

- Rat model of incisional wound
  - Improved collagen deposition
  - Accelerated neovascularization
  - Increased inducible nitric oxide synthase production
  - Increased cyclooxygenase-2 production
  - Faster resolution – levels reduced to normal sooner

CAFFEINE

- Methylxanthine properties
  - Antioxidant
  - Apoptotic
  - Immunomodulatory
  - UV-protective
  - Anti-carcinogenic
  - Inhibit epidermal growth factor

- Works complementary with green tea polyphenols

PENTOXIFYLLINE

• Methylxanthine derivative

• Inhibits fibroblast proliferation and collagen production in hypertrophic scars

• Increases collagenase activity

• Small study of patients with post-burn hypertrophic facial scarring showed pentoxifylline injections improved elasticity

Isaac et al BURNS 2009, Rawlins et al BURNS 2006, Isaac et al BURNS 2010
Fig. 5
Mouth opening – the dental distance (DD) in burnt individuals from treated group treated with 1 mg ml⁻¹ pentoxifylline and individuals from control group. Values of dental distance (DD) in mm ± SEM in pre- and after five weeks of treatment (p < 0.001).
CALCIUM CHANNEL BLOCKERS (CCB)

• Includes verapamil, diltiazem, amlodipine and nifedipine

• CCBs reduce TGF-β, other growth factors and interleukins
  • Affects fibroblasts and angiogenesis

• Block calcium influx into cells inhibits protein kinase C which reduces fibroblast production
  • Useful in second stage of healing to prevent keloid and hypertrophic scarring

VERAPAMIL

• Verapamil has been studied as topical and injection forms
  • Injections have similar efficacy to corticosteroids
  • Review showed positive results

• Verapamil gel produced good quality scars after surgery vs placebo
  • Mammoplasty: 80% vs. 48%
  • Abdominoplasty: 72% vs. 51.2%

AMLODIPINE

Figure 1. Time (days) Required for Complete Wound Healing After Application of Tested Compounds

Significant difference from control group is shown * (P < 0.001).

Hemmati et al Jundishapur J Nat Pharm Prod 2014
NIFEDIPINE & DILTIAZEM

- Most commonly used in anal fissures

- Multiple studies have shown high healing rates even after treatment failures with nitroglycerin

- 71 pts with chronic anal fissures
  - Diltiazem 2% ointment healed 51 pts in 2-3 months & 8 more healed after 8 more weeks

- 64 pts with chronic anal fissures
  - Nifedipine 0.5% ointment had an equivalent healing rate of 97% vs surgery

TRETINOIN

- Reduces abnormal matrix metalloproteinase expression in keloid fibroblasts
  - Limits keloid expansion
  - Reduces inflammation
  - Affects collagen production

- Improves skin elasticity

- Increases angiogenesis

TRETINOIN

• Used in burns and acne scars

• 15 patients 2 years post-burn
  • Improved appearance and skin elasticity

• Adverse effects are common
  • Erythema, peeling, dryness and itching

TAMOXIFEN

• Inhibits TGF-β1 release to reduce fibroblast proliferation and collagen production

• 18 patients with keloid scars treated for 6 months
  • Significant reduction in lesion size

• 46 patients with hypertrophic burn scars for 6 months had significant improvement

TRANILAST

- Multiple studies have shown prevention or improvement of keloid and hypertrophic scars
  - Mostly in vitro or rat studies however

- Thought to work by inhibiting collagen production

- Inhibits metalloproteinase activity

## SUMMARY & DOSAGES

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta glucan</td>
<td>0.25-0.5%</td>
</tr>
<tr>
<td>MSM</td>
<td>2-5%</td>
</tr>
<tr>
<td>Aloe</td>
<td>0.2-2%</td>
</tr>
<tr>
<td>EGCg</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>Caffeine</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>0.3-1%</td>
</tr>
<tr>
<td>Agent</td>
<td>Dosage</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Verapamil</td>
<td>10%</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>1%</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>2%</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.5%</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>0.025-0.1%</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>0.1%</td>
</tr>
<tr>
<td>Tranilast</td>
<td>0.5-2%</td>
</tr>
</tbody>
</table>
Chauncey maintained one posture after the unfortunate rocking chair incident.
PAIN OR INFECTION CONCERNS

- Pain – can add to healing agents if needed
  - Local anesthetics
    - Bupivacaine 1%
    - Lidocaine 1%
  - Ketoprofen 5%
  - Gabapentin 6%

- Infection
  - Some of the healing agents seem to have antibacterial activity – e.g. phenytoin, sucralfate
  - Mupirocin 1-2%
  - Metronidazole 1-4%
COMBINING AGENTS
TREATMENT FREQUENCY & DURATION

• Usually twice daily application
  • Exception is tretinoin – up to once a day as tolerated

• Prevention with wounds or after surgery: 1-3 months
  • Hypertrophic or keloid: 30-60 days
  • Useful for burns to prevent contracture

• Treatment: 6-12 months
  • Atrophic & striae – can take over a year
  • Almost impossible to treat keloid scars
CASE STUDY: SURGICAL WOUND

- Hillary is a 48 yo woman who had surgery this week on her arm
- She has a history of hypertrophic scarring and is worried about developing a scar

- What would be a good combination to speed wound healing and help prevent risk of scarring?
Well, I've got good news and bad news.

The good news is that we've managed to reattach the head.
POSSIBLE COMBINATIONS

- If no pain or sign of infection:
  - Misoprostol 0.0024%/nifedipine 5%/phenytoin sodium 2%/tranilast 1%
  - Ascorbic acid 2%/caffeine 1%/EGCg 1%/MSM 5%

- If she is experiencing pain at the site:
  - Aloe vera 0.2%/ketoprofen 2%/lidocaine 2%/misoprostol 0.0024%/phenytoin sodium 2%

- Pracaxi oil base with silicone or ointment reasonable base choices
HILLARY FOLLOW-UP

• What if Hillary had not sought treatment until a couple months after surgery?

• To treat her hypertrophic scars:
  • Pentoxifylline 0.3%/caffeine 1%/EGCg 1%
  • Caffeine 1%/tamoxifen 0.1%/tranilast 1%

• Pracaxi oil base with silicone or liposomal gel reasonable base choices

• Avoid steroids unless scar is older
CASE STUDY: DIABETIC ULCER

- Larry is a 73 yo man with a diabetic ulcer on his left foot that he’s had for six months
  - His circulation is poor and it is not healing
  - He doesn’t complain of pain due to decreased sensation from diabetic neuropathy
  - No sign of infection yet

- What combination of healing agents should we use to promote healing of the ulcer?
POSSIBLE COMBINATIONS

• Need to promote circulation and healing:
  • Misoprostol 0.0024%/nifedipine 5%/tranilast 1%
    • If ulceration is severe add phenytoin sodium 2%
  • Caffeine 1%/pentoxifylline 1%/tranilast 1%

• If becoming concerned about infection:
  • Metronidazole 2%/misoprostol 0.0024%/phenytoin 5%

• Pracaxi oil base with silicone, pluronic gel or ointment – consider dressing changes
CASE STUDY: BURN

- Casey is a 26 yo with radiation burns
  - Need to promote epithelization immediately
  - Goal: minimize scarring and pain

- What combinations would prevent contracture scarring and loss of elasticity?
POSSIBLE COMBINATIONS

• If pain is minimal:
  • Caffeine 1%/EGCg 1%/pentoxifylline 0.3%
  • Verapamil 10%
  • Ascorbic acid 2%/caffeine 1%/EGCg 1%/MSM 5%
  • Caffeine 1%/EGCg 1%/MSM 5%/tranilast 1%

• If severe:
  • Aloe vera 0.2%/ketoprofen 2%/lidocaine 2%/misoprostol 0.0024%/phenytoin 2%/sodium hyaluronate 0.5%/urea 10%

• Pracaxi oil base with silicone or ointment
QUESTIONS?

Thanks for coming!

If you have further questions, please feel free to contact me at:

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