PodiatryToday

GO

Utilizing Topical Compounded Medications To Modulate Wound Healing

Issue Number:
Volume 27 - Issue 8 - August 2014

Author(s): Allen Jacobs, DPM, FACFAS

Compounding topical medications can help tailor the treatment of wounds to individual patient needs and may offer wound healing effects that are not otherwise available. This author explores how compounded topical medication can reduce pain, stimulate new tissue healing, increase vascular perfusion and decrease bioburden.

Ulceration is a pathologic condition that not infrequently confronts podiatric physicians. Common causes of ulceration in podiatry

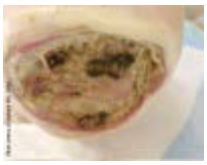
practices include ulceration secondary to venous insufficiency; decubitus ulceration, particularly on the posterior heel; ulceration associated with arterial insufficiency; mixed arteriovenous ulceration; and neuropathic ulcerations in patients with diabetes. Less commonly, ulceration is associated with malignancy, connective tissue disorder, hypertension or sickle cell anemia.

Since ulcerations may differ in their etiology, addressing the evaluation and specific treatment of ulceration does require consideration of etiologic factors that may be unique to the development of the ulceration. For example, venous ulceration, which typically occurs in the area of the medial malleolus, results from poor venous function with increased venous pressure. Treatment options include compression therapy, the use of skin grafts or skin graft substitutes, open or endovascular management of incompetent venous structures, sclerosis of the veins and, of course, wound care for management of the ulceration.

Constant unrelieved pressure causes decubitus ulcerations, resulting in a loss of blood supply and ischemia. We most often encounter this on the posterior aspect of the heel. The treatment of decubitus ulcerations frequently requires debridement and wound care as well as local flaps and grafts.

Arterial insufficiency ulceration results from a lack of perfusion with subsequent necrosis of tissue. These are more common on the lateral aspect of the ankle joint, are typically painful and are associated with the clinical signs and symptoms of peripheral arterial disease (PAD). The treatment of arterial ulcers typically includes restoration of the vascular supply, debridement and wound care, and often amputation.

Arteriovenous ulceration arises secondary to venous insufficiency in combination with PAD.



Neuropathic diabetic foot ulceration is associated with areas of increased pressure or injury unperceived by the patient with diabetes secondary to sensory neuropathy. Such ulcers are also associated with an increased incidence of vascular disease. The treatment of such ulcers includes removal of pressure and offloading, improvement in vascular supply, reduction of bioburden, debridement and local wound care.

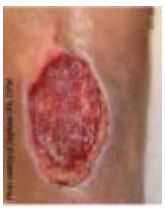
Extemporaneous compounding helps physicians individualize the treatment required for patient specific needs and create topical preparations that are not otherwise commercially available.[1] Topical compounded medications

for ulcer management are adjunctive and work in conjunction with other principles of good wound care such as pressure relief, debridement, revascularization or hyperbaric oxygen therapy in order to enhance healing.

Due to the varying etiologies of ulceration and the specific clinical presentation of each patient, the clinician must assess the unique needs of each patient and the particular clinical scenario. One would utilize compounded medications in the treatment of ulcerations when premade medications are insufficient or not available to meet those specific needs. Ultimately, the goal is the enhancement of wound healing.

The advantage of compounding medications in the treatment of wounds is that the treatment is site directed, and not dependent on systemic circulation. Therefore, in the presence of decreased vascular perfusion, topically applied medications may achieve therapeutic benefits that would not otherwise occur if one administered the same medication systemically. Examples might include medications such as pentoxifylline (Trental, Sanofi Aventis).

In addition, adherence is easier when one topical medication is required for the treatment of the wound rather than the application of multiple preparations. Such an example would include patients who require collagenase for debridement and perhaps a topical antiseptic or antibiotic. With topical compounded therapy, one can combine these medications into one cream or ointment, which also offers the potential for reduced wound care costs.



The contents of any particular compounded medication for enhancement of wound healing depend on what the healthcare provider perceives as the needs of each patient. Compounding offers the advantage of wound manipulation and manipulation of the actual healing process rather than attempting to determine what premade product would be applicable for a particular patient. Compounding allows for the individual's age and for wound care tailored to each patient.

When one applies topical agents at the site of the wound, these agents act locally and there is increased local concentration in comparison to when a clinician administers the same medication systemically. Compounding offers the ability to alter local wound dynamics.

As an aside, the decision to utilize a drug in an off-label manner is a matter of medical judgment and not one of regulatory approval. The Federal Food, Drug And Cosmetic Act does not limit the manner in which a physician utilizes an approved drug.[2]

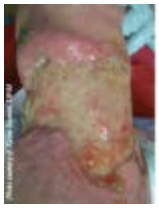
How Topical Compounded Medications Can Enhance Wound Healing

Topically applied medications may provide stimulation of epithelialization, stimulation of granulation tissue, upregulation of growth factors and reduction of bioburden. Topical medications may increase vascular perfusion to the wound, help achieve debridement and help reduce pain.

Typically, wound healing consists of a series of stages that hopefully result in healing of the wound. The stages include initial hemostasis, an inflammatory stage, a stage of angiogenesis, the formation of granulation tissue, epithelialization and eventually remodeling of the wound.

Compounding allows for the concurrent administration of medications including anesthetics to reduce pain, antibiotics or antiseptics to reduce bioburden, enzymes such as collagenase or urea for debridement of the wound, medications to stimulate granulation tissue and growth factors, as well as for moisture enhancement and balance.

Examples of medications that one can apply concurrently to achieve wound healing would include phenytoin (Dilantin, Pfizer), which promotes granulation tissue formation; misoprostol (Cytotec, Pfizer), which accelerates wound healing; metronidazole (Flagyl, Sanofi Aventis) to provide antimicrobial effects; and nifedipine (Procardia, Pfizer) to increase vascular perfusion. Although one could prescribe and utilize each component individually, one topically applied medication can achieve multiple benefits at the same time. Again, practitioners determine the specific components of each compounded topical medication for the treatment of wounds based upon the needs they perceive for each individual patient.



Other examples of components that one can apply within this same gel, ointment or cream include lidocaine for reduction of pain and increased blood flow to the wound; tea tree oil for an antifungal, antibacterial and anti-inflammatory effect; or pentoxifylline to provide improved blood viscosity and work synergistically with calcium channel blockers to increase blood flow to the wound.

Using Topical Agents To Bolster Debridement

Debridement involves the removal of the necrotic and nonviable tissue impeding wound healing. It also “restarts”

the wound healing process by converting the wound to a fresh, bleeding wound. One can perform debridement through a variety of techniques such as scalpel, curettes, ultrasound and hydrosurgery. One may employ topical agents for debridement when other methods of debridement are not appropriate or not feasible. Clinicians may also use topical agents following debridement in order to prevent or reduce the recurrence of nonviable tissue.

Topical collagenase may help treat wounds to remove the native collagen within eschars and necrotic tissue. Collagenase (Santyl, Smith and Nephew) also serves to sever peptide bindings in collagen. Typically, commercially available collagenase is available at a fixed dosage of 250U/gm. However, with compounding, the concentration of collagenase use may achieve a greater debridement effect.

Furthermore, other agents such as 10-30% urea may achieve further loosening of necrotic and nonviable tissue, and when one combines this urea agent with collagenase in the same compounded wound care product, the clinician can achieve a greater effect. Physicians commonly use collagenase in the management of wounds. When one utilizes collagenase in a compounded topical medication, it can be at the same or at greater strength than commercially available products.

Keys To Increasing Vascular Perfusion To The Wound

Not infrequently, increasing vascular perfusion to a wound is required. With the utilization of compounding, one may add agents that promote increased vascular perfusion to achieve greater blood flow to the wound. Examples would include the addition of nifedipine, pentoxifylline, verapamil (Calan, Pfizer), amide local anesthetics such as lidocaine (Lidocaine, Endo Pharmaceuticals) or other calcium channel blockers such as propranolol. Accordingly, one may utilize a compounding agent to increase blood flow and at the same time use a debriding agent, topical anti-inflammatory, antibiotic, or antiseptic through one medication.

Nifedipine and verapamil are other calcium channel blockers that relax blood vessels and increase blood flow to the wound. Calcium channel blockers prevent the release of internal calcium stores into cell cytosol, and as a result, the smooth muscle within the tunica media of the arterial supply does not respond to the calcium ion signal. This typically results in contracture of the muscle and decreased vascular perfusion.

Amide anesthetics such as lidocaine or bupivacaine (Marcaine) also act as calcium channel blockers, causing increased blood flow to the wound. Since they are local anesthetics, lidocaine or bupivacaine also reduce the vasoconstriction resulting from pain, leading to a vasodilatory effect.

Pentoxifylline is a xanthine derivative and phosphodiesterase inhibitor. It improves red blood cell deformability, resulting in increased oxygen delivery to the wound. It reduces blood viscosity, resulting in improved wound blood supply and the prevention of thrombus formation.

In regard to agents clinicians use to improve blood supply to a wound, these modalities may be particularly useful in treating arterial ulcers, arteriovenous ulcers, ulcerations associated with conditions such as sickle cell anemia or vasculitis-associated ulceration in connective tissue disorders such as scleroderma or systemic lupus erythematosus. In addition, these ulcers are typically painful and the utilization of a topical anesthetic together with other wound healing agents may be very helpful in reducing pain and the need for opioids or other analgesics.

How Compounding Can Bolster Collagen

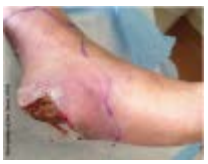
Fibroblasts produce collagen. In some disorders such as diabetes, fibroblasts have abnormal function or abnormal structure. Many wound dressings provide collagen for placement within a wound to provide a surface or scaffold on which cells might migrate and expedite wound healing.

With compounding, one may include collagen in the applied medication to provide the wound with collagen in addition to providing other wound healing stimulants at the same time.

What The Literature Reveals About Compounding Meds And Stimulating New Tissue Growth

Compounding allows the inclusion of agents that may be beneficial in stimulating the growth of new tissue. The most commonly included agents include phenytoin and manuka honey.
There is a great deal of literature supporting the use of phenytoin for the stimulation of new tissue growth in the treatment of wounds. Fourteen randomized controlled trials have demonstrated evidence that supports the use of

phenytoin for diabetic foot ulceration, venous ulceration and chronic wounds.[3] Researchers have shown that phenytoin stimulates collagen, protein and hydroxyproline synthesis; increases fibroblastic activity, monocyte and macrophage production of platelet-derived growth factors (PDGF); and increases interleukin-1 beta (IL-1β) and myofibroblasts, resulting in faster wound contracture.[4-6] Stimulation of the myofibroblasts results in faster wound contracture. The literature has also shown improved graft survival in wound management.[7]



Authors have also demonstrated that combining phenytoin with offloading and debridement in the management of chronic diabetic foot ulceration enhances healing.[8] Rhodes and colleagues found that phenytoin was superior to standard therapy, DuoDerm therapy (ConvaTec) or the topical application of triple antibiotics in the treatment of stage II decubitus ulcerations.[9] The therapeutic benefit of topical phenytoin for the treatment of venous ulceration is similarly evident.[10] Researchers have also found topical phenytoin to be beneficial for a variety of commonly encountered ulcerations.[11] The application of phenytoin following surgical excision of cutaneous melanotic lesions reportedly facilitates rapid healing and better cosmetic results.[12]

Manuka honey is a product produced from the nectar of the manuka tree, found in Australia and New Zealand. It was FDA approved for wound management in 2007. Researchers have shown that manuka honey promotes tissue growth and epithelialization, and has antibacterial properties as well.[13,14]

Misoprostol is a synthetic analog of prostaglandin E1 (PGE1). Misoprostol inhibits IL-1 and tumor necrosis factors. It also serves to promote collagen synthesis.[15] Misoprostol can improve the healing of venous ulcerations in comparison to compression and standard therapy alone.[16] Studies have also demonstrated that misoprostol decreases the healing time and increases the survival rate of local flaps utilized in the reconstruction of soft tissue defects.[17-19]

Reducing Pain And Wound Inflammation With Compounds

One may add local anesthetics to most compounded preparations. The addition of local anesthetics makes the manipulation of a wound less painful for patients by reducing the discomfort associated with many ulcers such as hypertensive ulcers, ischemic ulcers or ulcers associated with vasculitis. In addition, local anesthetics can serve to

increase blood flow to the wound by reducing the pain associated with vasoconstrictive phenomena.

Clinicians may add a variety of anti-inflammatories such as diclofenac (Voltaren, Novartis) or flurbiprofen (Ocufen, Allergan) to a compounded wound healing preparation to reduce inflammation and inflammation-associated pain. Anti-inflammatories work by inhibiting prostaglandin synthesis, which tissue injury induces and results in the lowering of the threshold for sensory nerves to activate and cause pain. The anti-inflammatories act by inhibiting arachidonic acid, preventing the formation of inducible prostaglandins, and offering the benefit of local anti-inflammatory activity without the risks associated with the systemic administration of anti-inflammatories.

How Topical Compounds Reduce Bioburden

Bioburden is generally described as the metabolic load imposed by bacteria on a wound bed.[20] The bacteria present within wounds utilize oxygen and nutrients, contributing to the production of free oxygen radicals and imbalances between matrix metalloproteinases and matrix metalloproteinase inhibitors. Bacteria also produce endotoxins and exotoxins, as well as proteases that act to damage the extracellular matrix, all of which interfere with wound healing. All chronic wounds heal in a colonized state.

Physicians may add antibiotics and antiseptics to compounded wound care preparations in order to reduce bacterial count. One may add antibiotics such as vancomycin, clindamycin, metronidazole, quinolone antibiotics or erythromycin to reduce bacterial count and prevent critical colonization, or even slow infection. In addition, antifungal activity may be enhanced within compounded wound care preparations utilizing medication such as terbinafine (Lamisil, Novartis), itraconazole (Sporanox, Janssen Pharmaceuticals) or nystatin (Nystop, Perrigo).

Tea tree oil may also be an addition to topical compounded wound care preparations. Tea tree oil has antibacterial, antifungal, antiviral and anti-inflammatory activity. It is useful for the treatment of methicllin-resistant *Staphylococcus aureus* (MRSA) as well as *Enterococci.*

In Conclusion

The utilization of topical compounded wound care preparations allows for a process driven manipulation of the wound rather than one that is product driven. Rather than

having to choose between the application of one or two topical preparations, compounding offers the opportunity to accomplish multiple physiologic effects simultaneously. Examples might include a combination of phenytoin to enhance tissue growth, lidocaine to reduce wound pain, collagen to enhance epithelialization and granulation, and nifedipine to increase vascular supply.

Dr. Jacobs is a Fellow of the American College of Foot and Ankle Surgeons, and a member of the Association of Physicians in Wound Healing. He is in private practice in St. Louis.

References

1. Chiu HY, Tsai TF. Topical use of systemic drugs in dermatology: a comprehensive review. *J Am Acad Derm.* 2011; 65(5):1048.e1-22.
2. Beck JM, Azari ED. FDA, off-label use and informed consent: debunking myths and misconceptions. *Food Drug Law.* 1998; 58(1):71-104.
3. Shaw J, Hughs CM, Lagan KM, Bell PM. *Br J Dermatol.* 2007; 157(5):997-1004.
4. Dill RE, Lacopino AM. Myofibroblasts in phenytoin-induced hyperplastic connective tissue in the rat and in human gingival overgrowth. *J Periodontol.* 1997; 68(4):375-80.
5. Iacopino AM, Doxey D, Cutler CW, et al. Phenytoin and cyclosporine: a specifically regulated macrophage phenotype and expression of platelet-derived growth factor and interleukin-1 in vitro and in vivo: possible molecular mechanism of drug-induced gingival hyperplasia. *J Periodontol.* 1997; 68(1):73-83.
6. Akalin FA, Bozkurt FY, Sengun D, et al. Hydroxyproline and total protein levels in gingiva from patients treated with phenytoin and cyclosporine-A. *J Nihon Univ Sch Dent.* 1996; 38(1):21-30.
7. Younes N, Albsoul A, Badran D, Obedi S. Wound bed preparation with 10 percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. *Dermatol Online J.* 2006; 12(6):5.
8. El-Nahas M, Gawish H, Trashoby M, State O. The impact of topical phenytoin on recalcitrant neuropathic diabetic foot ulceration. *J Wound Care*. 2009; 18(1):33-37.
9. Rhodes RS, Heyneman CA, Culbertson VL, et al. Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann Pharmacother.* 2001; 35(6):675-81.
10. Hokkam E, El-Labban G, Shams M, et al. The use of topical phenytoin for healing of chronic venous ulcerations. *Int J Surg.* 2011; 9(4):335-8.
11. Pendse AK, Sharma A, Sodani A, Hada S. Topical phenytoin in wound healing. *Int J Dermatol.* 1993; 32(2):214-

17.
12. Pereira CA, Alchorne Ade O. Assessment of the effect of phenytoin on cutaneous healing from excision of melanocytic nevi on the face and on the back. *BMC Dermatol.* 2010; 10:7.
13. Kilty SJ, Duval M, Chan FT, Ferris W, Slinger R. Methylglyoxal: (active agent of manuka honey) in vitro activity against bacterial biofilms. *Int Forum Allergy Rhinol.* 2011;1(5):348-50.
14. Majtan J, Klaudiny J, Bohova J, et al. Methylglyoxal-induced modifications of significant honeybee proteinous components in manuka honey: possible therapeutic implications. *Fitoterapia.* 2012; 83(4):671-7.
15. Vandervoort JM, Nieves MA, Fales-Williams A, et al. An investigation of misoprostol in the promotion of wound healing. *Vet Comp Orthop Traumatol.* 2006; 19(4):191-5.
16. Milio G, Mina C, Cospite V, et al. Efficacy of the treatment with prostaglandin E-1 in venous ulcers of the lower limbs. *J Vasc Surg.* 2005; 42(2):304-8.
17. Eskitascioglu T, Gunay GK. The effects of topical prostacyclin and prostaglandin E1 on flap survival after nicotine application in rats. *Ann Plastic Surg.* 2005; 55(2):202-6.
18. Mahoney J, Ponticello M, Nelson E, Ratz R. Topical misoprostol and wound healing in rats. *Wounds*. 2007; 19(12):32-37.
19. Sawada Y, Sugawara M, Hatayama I, Sone K. A study of topical and systemic prostaglandin E1 and survival of experimental skin flaps. *Br J Plastic Surg.* 1993; 46(6):670-2.
20. Warriner R, Burrell R. Infection and the chronic wound: a focus on silver. *Adv Skin Wound Care.* 2005; 18(1):2-12.

Add new comment

Your name

E-mail

Homepage

Comment *

What code is in the image? *

Save Preview

MOST POPULAR ARTICLES THIS WEEK

How To Complete Diabetic Shoe Medicare Forms Correctly
Marty Chalfin, CPed
1,449 reads | 0 Comments

Current Insights On PRP And Achilles Tendinopathy
Lawrence M. Oloff, DPM, FACFAS
1,061 reads | 0 Comments

A Guide To Conservative Care For Plantar Fasciitis
Brian Fullem, DPM
3,051 reads | 0 Comments

In The Midst Of Hate, A Plea For Kindness
Jeffrey D. Lehrman DPM FASPS
819 reads | 0 Comments

Case Studies With Pyogenic Granulomas
Nicholas A Campitelli DPM FACFAS
582 reads | 0 Comments

CURRENT FEATURES

When Is Heel Pain Nerve Pain?
Stephen Barrett, DPM, FACFAS
2,546 reads | 1 comments

How To Treat Haglund's Deformity In Runners
Troy Boffeli, DPM, FACFAS, and Sam Gervais, DPM
1,833 reads | 0 comments

A Guide To Conservative Care For Plantar Fasciitis
Brian Fullem, DPM
3,051 reads | 0 comments

Current Insights On PRP And Achilles Tendinopathy
Lawrence M. Oloff, DPM, FACFAS
1,061 reads | 0 comments

Essential Tips On ICD-10 And Wound Care Coding
Jeffrey D. Lehrman, DPM, FASPS, MAPWCA
1,326 reads | 0 comments

More Current Features

TOPIC CENTER

Achilles Tendonitis
AFO
Amputation
Ankle Arthrodesis
Ankle Replacement
Athletic Shoes
Bioengineered Alternative Tissues
Biomechanics
Bunionectomy
Calcaneal Fractures
Charcot
Coding
Custom Orthosis
Dermatology
Diabetic Foot
Diabetic Foot Infection
Diabetic Foot Ulcer
Diabetic Peripheral Neuropathy
EMR/EHR
Fall Prevention
Flatfoot
Hallux Valgus
Hammertoe
HBOT
Heel Pain
Jones Fracture
Limb Salvage
Metatarsal Fractures
MRSA
NPWT
Offloading
Onychomycosis
Orthotics
Osteomyelitis
PAD
Peripheral Neuropathy
Plantar Fasciitis
Practice Management
Pressure Ulcers
Sever's Disease
Split Thickness Skin Grafts
Sports Medicine
Staff Management
Stress Fractures
Tinea Pedis
Venous Ulcers
Wound Care
Wound Debridement
Wound Dressings

POLL

How many visits do you see a patient before scheduling bunion surgery?

○ 1

- 2-4
- 5+

Vote

UPCOMING MEETINGS

Windy City Podiatry Conference
December 2, 2016 to December 4, 2016
Chicago, IL, United States

Global Foot and Ankle Symposium
December 2, 2016 to December 3, 2016
New York City, NY, United States

Foot and Ankle Business Innovations
January 27, 2017 to January 29, 2017
Chicago, IL, United States

More Upcoming Events

Back to top

PodiatryToday

SOCIAL

facebook
twitter
linkedin
RSS Feed