WOUND Management

Continuing Medical Education

The Effects of Medications in Wound Healing

What drugs your patient takes may influence this process.

Objectives

1) Recognize key features present during the complex process of dermal wound healing.

2) Appreciate the various biochemical, cellular, and immunological reaction cascades present during dermal wound healing.

3) Appreciate the clinical data regarding relative pharmacological effects of specific medication classes on the phases of wound healing as found in the literature.

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*Following this article, an answer sheet and full set of instructions are provided (p. 204).—**Editor***

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Introduction

Wound healing disorders present a serious clinical problem and are likely to increase because of their association with diseases such as diabetes, hypertension, and obesity. It is acknowledged that prescription medications are a vital component in the effort to maintain or improve health of individuals suffering from these diseases. Utilization of prescription medications is particularly high among older individuals and those patients with chronic medical conditions. Moreover, the most recent data from a sample population survey of United States civilian households reveals that 45.3% of the population consumes at least one prescription drug a month, while 17.7% of the population consumes three or more prescriptions a month.[1]

Hess and Kirsner report that approximately 1% of the world's general population and an estimated 2.5 million Americans have venous leg ulcers.[2] Prevalence data describing the etiology of at least one foot ulcer among the 20.8 million Americans who have diabetes has been estimated to be between 12.7%-15%.[3,4] Further, in the United States, approximately 60% of all lower extremity amputations occur among persons with diabetes; of these lower extremity amputations, a foot ulcer preceded the resulting amputation by 85%.[4]

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Reflection of these prevalence statistics collectively allows for an inference and summation that an overlapping cross-sectional population exists as it pertains to concurrent use of prescription medications and patients with lower extremity wounds. Given that many healthcare providers overlook or are unaware of specific pharmacology and potential drug interactions, it is important that a clinician be knowledgeable of the existence of pharmacological interactions, either beneficial or harmful, between a patient's medication consumption and the potential effects on the wound healing process.

The purpose of this review is to offer the podiatric physician information regarding wound pharmacology: "drug and physiology" effects within the context of the wound healing process. In order to accomplish this endeavor, two concepts must be exemplified. An overview of basic wound healing physiology will be first offered because achieving this understanding is essential when discussing the effects of medications on the wound healing process. Secondly, building upon this foundation of wound healing physiology, potential drug and wound environment physiology effects as cited in the medical literature will be offered both as a narrative and as a graphic table to accentuate these effects.

Wound Healing Process Overview

Once a wound occurs, a multitude of biological and chemical processes take place. The wound healing response is aimed at restoring the tissue to its original integrity. The complex healing process of an acute dermal wound can be divided into three non-linear, overlapping phases of inflammatory reaction, proliferation, and remodeling.[5] Each phase lasts a specific length of time and has characteristic cellular elements. Karukonda, et al. have included both phenomenon of "injury' and "coagulation" into the wound healing sequence resulting in five sequential phases: injury, coagulation, inflammation, tissue formation and tissue remodeling.[6] Figure 1 illustrates this cascade defining each phase and the major elements involved within the wound healing sequence.

In order to balance degrading processes with the regenerative processes, these events require a finely tuned control of various biochemical, cellular, and immunological reaction cascades. This process is strictly regulated by multiple growth factors and cytokines released at the site of dermal injury. These cytokines and growth factors include: platelet-derived growth factor (PDGF), transforming growth factor alpha (TGF-α), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), ker-

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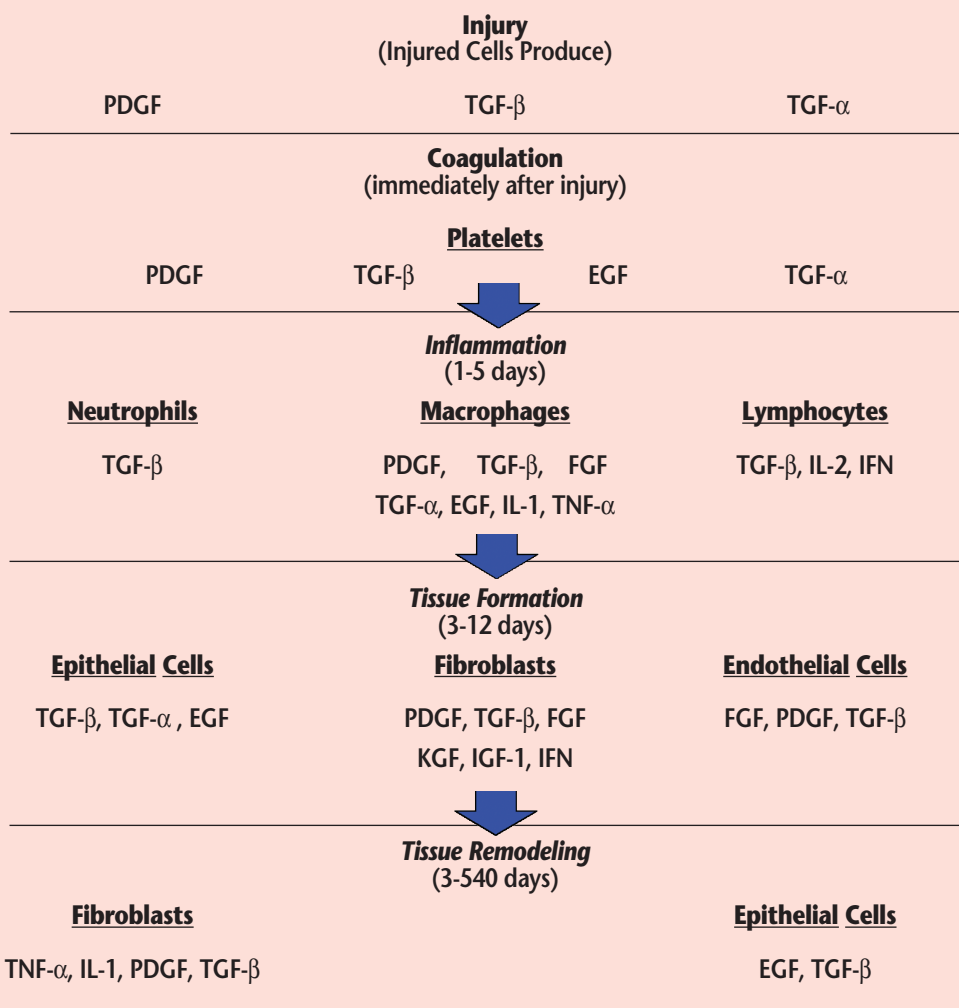
FIGURE 1
Wound Healing Process



Adapted from Karukonda SRK. Flynn TC, Boh EE, et al. The effects of drugs on wound healing: part 1. Intern J Dermatol 2000; 39 (4): 250-257.

atinocyte growth factors (KGF), insulin-like growth factor (IGF-1), tumor necrosis factor alpha, (TNF-α), interleukin-1 (IL-1), interleukin-2 (IL-2), and interferon (IFN). These growth factors, their sources, and their relative wound healing functions are summarized and presented graphically in Table 1.

It appears that the balance of these cytokines, rather than their mere presence or absence, plays a decisive role in regulating the initiation, progression, and resolution of wounds. Individual cytokines can influence wound repair in different ways as they may have diverse effects in similar physiological situations and usually have more than one specific effect on cells. By intentionally or unintentionally manipulating the actions of growth factors and cytokines, the process of wound healing may be accelerated or modified.

The inflammatory response lasts 24-48 hours and is characterized by warmth, redness, and pain. This phase occurs in the first one to four days of injury. Essentially, the inflammation phase cleans the wound of dead cellular material and bacterial infection and sets up chemical gradients in the wound space. During this phase, blood enters the wound and signaling processes are enabled that give rise to the activation of clotting cascades and aggregation of macrophages and leucocytes, amongst other substances. Instantly, upon injury, blood coagulation and platelet aggregation form a fibrin clot as a provisional matrix for the migration of inflammatory cells and fibroblasts.

Within minutes neutrophils invade the wound, followed by monocytes and lymphocytes releasing large numbers of cytokines, which promote the migration, proliferation, and survival of various

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TABLE 1
Wound Healing Growth Factors and Functions

Growth Factors	Names	Sources	Wound Healing Functions
PDGF	platelet-derived growth factor	Platelets, Macrophages, Endothelial Cells Injured Cells	Chemotaxis Fibroblast Proliferation Collagenase Production
TGF-β	transforming growth factor beta	Platelets, Macrophages, Endothelial cells Epithelial cells, Neutrophils, Fibroblasts, Lymphocytes, Injured Cells	Chemotaxis Fibroblast Proliferation Collagen Metabolism
EGF	epidermal growth factor	Plasma, Platelets, Macrophages Epithelial Cells	Epithelial Cell Proliferation Granulation Tissue Formation
TGF-α	transforming growth factor alpha	Activated Macrophages, Platelets, Epithelial Cells, Injured Cells	Epithelial Cell Proliferation Granulation Tissue formation
KGF	keratinocyte growth factor	Fibroblasts	Epithelial Cell Proliferation
IL-1	interleukin-I	Macrophages	Fibroblast Proliferation
FGF	fibroblast growth factor	Pituitary, Macrophages, Fibroblasts Endothelial Cells	Fibroblast Proliferation Matrix Depositition Angiogenesis Wound Contraction
TNF-α	tumor necrosis factor-alpha	Macrophages, T-Lymphocytes	Fibroblast Proliferation
IGF-1	insulin-like growth factor	Plasma, Liver, Fibroblasts	Fibroblast Proliferation Synthesis of Collagen Synthesis of Proteoglycans
IFNs	interferon	Lymphocytes, Fibroblasts	Inhibition Fibroblast Proliferation Synthesis of Collagen

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cell types at the wound site.[7] These cell lines not only secrete proteinases and reactive oxygen species to defend against contaminating bacteria but also they are responsible for the phagocytosis of cell debris.[7] Leukocytes clear contamination by phagocytosis, thus creating favorable conditions for

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TABLE 2
Medication Effects on Wound Healing

Class	Mechanism	Effects on Wound Healing
Antibiotics (General)	Anti-infective	Removal of inflammation caused by infection
Tetracycline	Anti-infective- Anti-inflammatory	Inhibition leukocyte chemotaxis
Erythromycin	Anti-infective- Anti-inflammatory	Inhibition leukocyte chemotaxis
Neomycin	Anti-infective-Gram positive	Re-epithelialization promoted
Polymyxin-B	Anti-infective-Gram negative	Re-epithelialization promoted
Bacitracin	Anti-infective-Gram positive	Re-epithelialization promoted and Contraction Inhibited
Gentamicin	Anti-infective-Gram negative	Re-epithelialization delayed
Mupirocin	Anti-infective-Gram positive	Contraction Inhibited
Silver sulfadiazine	Anti-infective-Gram positive	Re-epithelialization promoted
	Anti-infective-Gram negative	Contraction mildly Inhibited
	Candida, fungi, Herpes simplex	
Antiseptics (General)	Topical disinfective	Degrees of Cytotoxicity
Povidone iodine	Topical disinfective	Mild decrease of Contraction
Ethyl alcohol		Re-epithelialization inhibited
Acetic acid 0.025%	Anti-infective-P aeruginosa	Re-epithelialization inhibited and Contraction Inhibited
Anticoagulants	Inhibit coagulation cascade intrinsic and extrinsic pathways	Prevents fibrin deposition avoids injury and inflammation
Antiplatelet drugs	Inhibit platelet aggregation	Inhibition of inflammation mediated by arachidonic
	Inhibit arachidonic acid pathway	acid metabolites
Corticosteroids	Inhibition of gene expression	Decrease Inflammatory mediators Decrease platelet adhesion Decrease WBC recruitment and phagocytosis Decrease tissue formation Decrease tissue remodeling
Colchicine	Inhibition of microtubule formation	Decrease cytokine release Decrease granulocyte migration Decrease blood supply from vasoconstriction Decrease fibroblast activity Interrupted excellular transport of procollagen Increase collagenase synthesis
Vasoconstrictors (cocaine-epinephrine)	Impaired microcirculation	Increase ulcer necrosis
Smoking (Nicotine)		Increase scarring
Ascorbic Acid (deficiency)	Essential cofactor for hydroxylation of proline and lysine	Poor wound healing due to impaired collagen synthesis

angiogenesis, cell migration, and cell proliferation.[8] The macrophages are the most important inflammatory cell in wound healing.[6,8] Macrophage-derived cytokines are essential for the initiation and propagation of new tissue formation.[6,8]

Once the wound has been cleaned and prepared by the inflammatory phase, the process of healing can begin. The proliferative phase of wound healing is dominated by cellular activity and repair of tissue and occurs between 3-12 days.[6] Within 48-72 hours of the initial injury, fibroblasts migrate into the damage area. The proliferative phase is characterized by the formation of granulation tissue as macrophages, fibroblasts, inflammatory cells, new capillaries embedded in a loose extracellular matrix of collagen, fibronectin and hyaluronic acid move into the wound space.[6] Macrophages continue to remain the source of cytokines for fibroplasia and angiogenesis.[6] Fibronectin is an extracellular matrix macromolecule, and is used to model the extracellular matrix.

During fibroplasia, new dermal matrix and granulation tissue form. As fibroplasia takes place, the process of angiogenesis is initiated by the release of growth factors. Re-epithelialization begins during this phase to form a new layer of skin over the wound. Fibroblasts are involved in wound contraction, fibronectin production, and collagen accumulation.

Remodeling

The final phase of wound healing is characterized by the gradual replacement of granulation tissue by connective tissue. This regeneration phase involves the growth of capillaries, fibroblasts, and epithelium into the wound site for building up new tissue. This process requires locally acting cytokines. However, little is known about the factors and mechanisms that eventually restrain tissue growth once the repair process has been completed. The synthesis of collagen and proteinase inhibitors is stimulated, among other things, by TGF-β and related factors. The extracellular matrix is formed in a loose manner and is relatively weak. Maturation involves remodeling of the extracellular matrix and continuing collagen deposition, which adds to the strength of the resulting scar tissue. Gradual reduction in vasculature and cellular structure ensues.

Wound Contraction

Wound contraction occurs in full-thickness wounds and reaches a peak between 5 to 15 days after the injury.[6] During the second week of healing, fibroblasts assume a myofibroblast phenotype characterized by large bundles of actin-containing microfilaments.[8] Contraction of the wound is mediated by myofibroblasts.[6,8,9] Closing of the wound and the evolution of a scar is associated with a striking decrease in cellularity, including disappearance of typical myofibroblasts. It has been suggested that cell death by apoptosis is the mechanism responsible for the evolution of granulation tissue into a scar. This phase lasts in a highly active state for around one year, but remodeling continues indefinitely.

There is evidence that non-steroidal anti-inflammatory drugs delay both epithelialization and angiogenesis in the early phases of wound healing.

The wound gains only about 20% of its final strength in the first three weeks.[8] The final strength of the wound is around 70-80% of that of uninjured tissue. The newly formed tissue is extremely delicate and supersensitive to external influences, especially pharmacological effects of specific classes of medications.

Interactions Between Medications and the Wound Healing Process

Medications may exert their effect by either assisting or interfering with the specific phases of wound healing. The effect of a particular medication on the wound healing process may depend on its respected mechanism of action, dosage, and route of administration in relation to the specific phase of the wound healing process.[10] Specific medication classes of particular interest to the podiatric physician regarding their effect on the wound healing process include: antibiotics, antiseptics, anticoagulants, antiplatelets, anti-inflammatory agents (specifically corticosteroids and colchicines), non-steroidal anti-inflammatory agents, and miscellaneous products.[9,10] The actions and effects of these medications on the wound healing process are depicted in Table 2.

Antibiotics

First of all, antibiotics should only be used in the presence of active infection. Secondly, all wounds are contaminated or colonized with bacteria and do not necessarily replicate to reach sufficient quantitative levels (105 CFU/gm) of tissue proven to compromise normal wound healing. Lastly, antimicrobial selection should be guided by both culture and sensitivity tests. When the podiatric physician elects to employ a particular antibiotic, the potential for side-effects should be monitored. In order to avoid the potential for the incidence of resistant organisms the prolonged use of topical antibiotics is discouraged.[11]

Karukonda, et al.[10] build on the foundation set forth by Smack, et al.[12] as they make the assertion that the benefit of topical antibiotic ointments is due to their vehicles. Re-epithelialization has been shown to be enhanced by the use of topical ointments and creams containing neomycin, polymixin B, neosporin, and silver sulfadiazine.[10,13]

Finally, it should be remembered that both tetracycline and erythromycin both demonstrate anti-inflammatory properties through the inhibition of leukocyte chemotaxis.[6,10,14,15]

Antiseptics

Ryan defines antiseptics as disinfectants used on body surfaces to reduce the number of normal flora

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and pathogenic contaminants.[16] Antiseptics can be considered nonselective dilute disinfectants; therefore, they can be toxic to host tissues.[17,18] Antiseptics are unlike antibiotics, which selectively act on a specific target; these agents function as nonspecific broad-spectrum microbial inhibitors without a specific cellular target site.[17,19]

Many advocates of antiseptic use proclaim that the use of an antiseptic solution on a traumatic wound decreases demands on the host defense system by reducing bacterial burden.

All antiseptics function similarly by damaging the cell wall or cell membrane of the pathogen, causing changes in permeability. Antiseptics are toxic to some bacteria, spores, fungi, and viruses, as well as host cells, such as leukocytes, erythrocytes, fibroblasts, keratinocytes, and osteocytes. Solutions with bactericidal and detergent properties have anticellular effects that may impede wound healing. An ideal antiseptic has the following properties: a broad spectrum of activity, a low potential for resistance, rapid activity, nonirritant or non-sensitizing, effective in the presence of cellular debris, and nontoxic.[17,20]

Lawrence states that the merits of irrigation fluids have received little scientific study and further emphasizes that the choice of an antiseptic is based on the balance between its bactericidal or bacteriostatic effectiveness and the degree of damage it might cause to healthy tissue.[17,21] Also, before selecting an antiseptic, Brennan and Leaper advise balancing potential antimicrobial benefits with potential cellular toxicity.[22]

Anglen argues that the evidence for the use of antiseptics in surgical wounds and the resulting lower infection rates are not convincing and substantial evidence suggest that wounds can be damaged by antiseptic use.[23] Furthermore, Anglen asserts, given that animal and clinical studies of the use of antiseptics in contaminated wounds have yielded conflicting outcomes, antiseptic irrigation should not be used because it offers risks without demonstrating benefits.[23]

Dulecki and Pieper reviewed the literature regarding irrigating acute traumatic wounds and concluded that normal saline solution is the most commonly used product because its cost-effectiveness, availability, and isotonic properties allow for it to be the least toxic to exposed tissues.[24]

The adverse effects of antiseptic use on healing wounds include tissue necrosis, increased intensity and duration of inflammation secondary to irritant contact dermatitis,[10,25] increased leukocyte, keratinocyte, and fibroblast cytotoxicity,[10,26] decreased epithelialization,[10,27-29] decreased wound strength, and decreased wound contraction.[10,28,29]

Most human clinical trials have found that antiseptics seem to be safe and not detrimental to wound healing. Specifically, povidone-iodine poses no significant hazard to wound healing.[17] Controversy still surrounds the use of other antiseptic agents because of the lack of sufficient number of human studies to be accepted as clinically based evidence. Until this evidence becomes available, the indiscriminate use of acetic acid, hydrogen peroxide, and sodium hypochlorite should be carefully evaluated by the podiatric physician when treating wounds.[17]

Anticoagulants and Antiplatelets

Anticoagulants of particular interest to the podiatric physician would be oral warfarin and heparin injection indicated for the prophylaxis and treatment of venous thrombosis and its extension.[10] Warfarin inhibits hepatic synthesis of vitamin K factors II, VII, IX, and X. Heparin, along with its cofactor antithrombin III, inactivates factors IX, X, Xa, XI, XII, and thrombin, thus inhibiting fibrinogen conversion to fibrin. Given the lack of clinical base data, it has been speculated that both warfarin and heparin may delay wound healing due to a lack of fibrin formation.[10,11]

One of the most popular antiplatelet medications is acetylsalicylic acid or aspirin. It inhibits platelet aggregation by irreversibly acetylating platelet enzymes that synthesize the precursors of prostaglandins and thromboxane A2. The effect of aspirin on cyclooxygenase lasts about 8-12 days, about the lifespan of a platelet. This anti-platelet effect is observed even with low dose aspirin 81 mg, once a day. Aspirin decreases both the inflammatory response and the acid mucopolysaccharide synthesis in wounds.[10,30] Both anticoagulants and anti-platelets are medications that may enhance hematoma formation. A hematoma is an excellent medium for microorganism growth as well as disrupting tissue structures, thus creating a hypoxic environment for the surrounding tissues, causing poor wound healing.[6,31]

Anti-inflammatory Agents

Corticosteroids affect cells by altering gene expression after crossing the cell membrane. They bind to cytoplasmic receptors and translocate into the cell nucleus. The inhibitory effect on gene expression over many cells allows for corticosteroids to affect almost every phase of wound healing.[10] The degree of inhibition of gene expression is related to the corticosteroid's potency. The most prominent effects are noticed when corticosteroids are administered during the early inflammatory phase.[10]

In the inflammatory phase of wound healing, corticosteroids inhibit prostaglandin synthesis.[11] There is a delay in the removal of bacteria and foreign bodies because both recruitment and phagocytic properties of neutrophils and macrophages are decreased.[32,33] A decrease in both epithelial regeneration and granulation tissue is caused by antimitotic activity.[11] Granulation tissue formation is reduced due to a decrease in fibroblast proliferation resulting in less collagen, less proteoglycans, and less glycosaminoglycans.[10] The reduced rate of keratinocyte proliferation and an increase in their rate of differentiation results in a thinned epidermis.[34]

Zitelli reported that oral doses of prednisone above 10 mg per day adversely affect wound healing during the first three days, while higher doses of 40 mg per day affect fibroplasia and collagen remodeling during subsequent days of wound healing.[35] Finally, the inhibition of wound contraction by corticosteroids

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in open wounds occurs regardless of their administration time.[36]

Colchicine affects wound healing by depolymerizing microtubules of mitotic spindles. Without microtubules, granulocyte migration is affected in the early inflammatory phase.[10] Fibroplasia is inhibited due to a decrease in collagen synthesis. Also, the blood supply to the wound may be compromised by colchicine vasoconstrictive effects.[10]

With the loss of microtubules, pro-collagen cannot be transported extracellularly from the fibroblast, thus halting the synthesis of collagen. Lastly, colchicine affects collagen remodeling by the increased synthesis of collagenase and increased collagenolytic activity, which result in decreased wound-breaking strength.[10]

Non-steroidal Anti-Inflammatory Agents

Non-steroidal anti-inflammatory agents inhibit both cyclooxygenase as well as lipooxygenase transformations of arachidonic acid, thus having more of an anti-inflammatory effect as opposed to an anti-platelet effect. The effects of ibuprofen and diclofenac on wound healing were examined by Dvidedi, et al. in experimental injuries in rats.[37] These drugs impede tissue repair by virtue of retarding inflammation.[37] There was 16-36% reduction in wound strength measured in terms of tensile strength in experimental rats.37 The detrimental effect of anti-inflammatory drugs was confirmed by histological examination of the wounds and by measurement of dry granuloma weight.[37]

Krischak, et al, examined the influence of diclofenac on incisional wound healing in ten male Wistar rats.[38] The rats received 5 mg. diclofenac per kg. bodyweight per day. Histomorphometry revealed a significant reduction in fibroblasts after diclofenac application compared with the placebo group. Further, epidermal thickness was not statistically different between the two groups.[38] Diclofenac diminished the amount of fibroblasts in connective tissue, reflecting the known anti-proliferative effect of diclofenac on fibroblasts.[38] Clinical healing was not affected. These authors recommend short-term diclofenac application to wounds for post-surgical and post-traumatic patients who would benefit from its antiphlogistic and analgesic effect.[38] However, if wound healing is disturbed, the negative effect of diclofenac on fibroblasts should be considered.[38]

These findings illustrate that there is evidence that non-steroidal anti-inflammatory drugs delay both epithelialization and angiogenesis in the early phases of wound healing because of an anti-proliferative effect; however, except for their dose-dependent effect on inflammation, non-steroidal anti-inflammatory agents have a limited role in wound healing.[10]

The podiatric physician must use sound medical judgment grounded in clinical-based evidence when deciding to employ the practice of off-label compounding to treat wounds.

Miscellaneous Medications

Those medications classified as vasoconstrictors, such as epinephrine, nicotine, and cocaine, can cause tissue hypoxia, thus affecting wound microcirculation and tissue formation.[6,10] Subcutaneous wound tissue oxygen tension was noted to be significantly reduced and remained low for 30-50 minutes after smoking.[39] Karukonda, et al. report that an increase in scarring has been noted in smokers when compared with nonsmokers.[10]

Vitamin C is a required co-factor for the hydroxylation of proline and lysine in order to synthesize normal collagen. In states of nutritional deficiency caused by starvation, illness and fad diets, ascorbic acid deficiency results, leading to poor wound healing due to impaired collagen synthesis. Alcoholism predisposes patients to nutritional deficiencies, but ethanol as a drug has not been proven to seriously affect wound healing.[6]

Benveniste and Thut examined the effect of chronic alcoholism on wound healing.[40] They demonstrated cell migration is slowed during the initial phases of wound healing, but cells do move into the healing wound and by day 30, there is no appreciable difference in cellular or collagen content.[6,40] However, Radek, et al. demonstrated in female rats that acute ethanol exposure impairs angiogenesis and the proliferative phase of wound healing.[41] This finding provides information regarding the effect of a single dose of ethanol on multiple parameters of the wound healing process.[41]

Off-Label Drugs

Finally, the concept of off-label prescribing of approved pharmaceuticals has created much attention as well as myths and misconceptions regarding its practice. There exist case studies found in the literature regarding the use of topical phenytoin to treat wounds. Phenytoin's main action on wound healing is its modification of collagen remodeling by decreasing collagenase reduction.[10] Also, collagen synthesis is not significantly affected by phenytoin, although it does inhibit wound contraction.[35] The podiatric physician must remember no uniform accepted specific guidance exists to assist clinicians trying to make decisions about the appropriateness of such prescribing. Given the lack of FDA approval for off-label uses, many off-label uses of drugs are published in the literature as case reports, allowing other clinicians the opportunity to use these treatments on a greater number of patients. The podiatric physician must use sound medical judgment grounded in clinical-based evidence when deciding to employ the practice of off-label compounding to treat wounds.

Conclusion

An understanding of the effects of medications in wound healing is essential. The purpose of this review

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was to offer the podiatric physician data regarding wound pharmacology within the context of the wound healing process. An overview of basic wound healing physiology was first offered to achieve an understanding of the effects of medications on the wound healing process. Secondly, building upon this foundation of wound healing physiology, potential drug and wound environment physiology interactions as cited in the medical literature were offered both as a narrative and as a graphic table to accentuate these effects. The podiatric physician must always employ clinical-based evidence when orchestrating the closure of wounds and be mindful that a patient's medication regimen may be influencing the wound healing outcome. ■

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Dr. Smith completed his postgraduate training with the College of Medicine at the University of Wales, Cardiff, Wales, UK in wound care and tissue repair. He is a member of the American Professional Wound Care Association and a consultant to the National Board of Podiatric Medical Examiners. He is a contributing editor and reviewer to JAPMA in the areas of podiatric clinical pharmacology and has authored 50 journal articles in the disciplines of pharmacy, podiatry, wound care. He currently practices in Ormond Beach, FL.

EXAMINATION

Continuing Medical Education

See answer sheet on page 205.

1) According to this review, what are the most important inflammatory cells in wound healing?
- A) Endothelial cells
- B) Neutrophils
- C) Macrophages
- D) Platelets

2) Karukonda, et al. included which two events in their model of the wound healing process?
- A) infection and sepsis
- B) injury and coagulation
- C) injury and sepsis
- D) ulceration and sepsis

3) Given that the source of keratinocyte growth factor (KGF) is fibroblasts, what is the wound healing function of keratinocyte growth factor (KGF)?
- A) Angiogenesis
- B) Synthesis of Collagen
- C) Matrix Deposition
- D) Epithelial cell proliferation

4) Wound contraction occurs in full thickness wounds and reaches a peak between _____ days after injury?
- A) 1 to 2
- B) 40 to 160
- C) 5 to 15
- D) 10 to 45

5) Karukonda, et al. and Smack, et al. assert that the benefit of topical antibiotics is due to their_____
- A) vehicles
- B) frequency of application
- C) strength of the antibiotic
- D) broad spectrum

6) Adverse effects of antiseptic use on healing wounds include:
- A) decreased wound strength
- B) leukocyte, keratinocyte, and fibroblast cytotoxicity
- C) decreased epithelialization
- D) all of the above are adverse effects

7) The effects of aspirin in a patient with a wound would be a decrease in both
- A) infection and wound sepsis
- B) increase in platelet aggregation
- C) the inflammatory response and acid mucopolysaccharide synthesis
- D) increase in wound strength

8) According to this review, what two antibiotics demonstrate anti-inflammatory properties through the inhibition of leukocyte chemotaxis?
- A) Penicillin and Ampicillin
- B) Acyclovir and Atrovaqone
- C) Tetracycline and Erythromycin
- D) Penicillin and Cephalexin

9) In the inflammatory phase of wound healing, corticosteroids inhibit_____ synthesis?
- A) thromboxane A1
- B) prostaglandins
- C) thromboxane B4
- D) antithrombin III

10) Corticosteroid-induced thin epidermis is a result of _____
- A) microtubes granulocyte migration
- B) anti-infective properties of anti-inflammatory agents
- C) inflammatory response
- D) reduced rate of keratinocyte proliferation and increased rate of their differentiation.

11) In Krischak, et al.'s investigation, their histomorphometry revealed a significant reduction_____.
- A) in fibroblasts after diclofenac application
- B) in macrophages after diclofenac application
- C) in scarring after diclofenac application
- D) in keratinocytes after diclofenac application

12) Colchicine affects wound healing by _____.
- A) remodeling microtubules of mitotic spindles.
- B) repolymerizing microtubules of mitotic spindles.
- C) depolymerizing microtubules of mitotic spindles.
- D) degrading and destroying fibroblasts through antifungal mechanism

13) Karukonda, et al.'s report comparing wound healing changes in smokers found
- A) increase of bleeding with smokers
- B) increase in scarring
- C) increase in wound tensile strength
- D) increase in infection

14) Radek, et al. demonstrated in female rats that acute ethanol exposure
- A) impairs wound closure
- B) impairs wound tensile strength
- C) impairs angiogenesis and the proliferative phase
- D) impairs infection

Continued on page 204

Continuing Medical Education

EXAMINATION

(cont'd)

15) The wound healing function of platelet-derived growth factor include:
- **A) Chemotaxis**
- **B) Fibroblast Proliferation**
- **C) Collagenase Production**
- **D) All are functions of PDGF**

16) Phenytoin's main action on wound healing is its modification of collagen remodeling by
- **A) increasing collagenase reduction**
- **B) decreasing collagenase reduction**
- **C) decreasing collagenase production**
- **D) increasing collagenase and extracellular matrix degradation**

17) The required co-factor for the hydroxylation of proline and lysine in order to synthesis normal collagen is?
- **A) Thiamine**
- **B) Pyridoxine**
- **C) Ascorbic acid**
- **D) Folic acid**

18) Antiseptics can be considered to be _____; therefore they can be toxic to host tissue.
- **A) non-selective dilute disinfectants**
- **B) non-selective dilute antibiotics**
- **C) non-selective concentrated disinfectants**
- **D) selective dilute disinfectants**

19) The inflammatory response lasts 24-48 hours and is characterized by
- **A) coldness, whiteness, and pain**
- **B) redness, pain, and coldness**
- **C) warmth, redness, and pain**
- **D) warmth, coldness, pain, paleness**

20) Injured cells release these substances during injury:
- **A) PDGF**
- **B) TGF-β**
- **C) TGF-α**
- **D) All the above are released**

See answer sheet on page 205.

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The Effects of Medications in Wound Healing

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2.	A	B	C	D	12.	A	B	C	D
3.	A	B	C	D	13.	A	B	C	D
4.	A	B	C	D	14.	A	B	C	D
5.	A	B	C	D	15.	A	B	C	D
6.	A	B	C	D	16.	A	B	C	D
7.	A	B	C	D	17.	A	B	C	D
8.	A	B	C	D	18.	A	B	C	D
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