CLINICAL MANAGEMENT extra

The Effect of Oral Medication on Wound Healing

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GENERAL PURPOSE:

The purpose of this learning activity is to provide information about the effects of oral medications on wound healing.

TARGET AUDIENCE:

This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES:

After participating in this educational activity, the participant should be better able to:

1. Identify oral medications that aid in wound healing.

2. Recognize oral medications that interfere with wound healing.

ABSTRACT

Given the accelerated medical discoveries of recent decades, there is a surprising lack of oral medications that directly improve wound healing. Of the oral medications available, most target ancillary aspects of wound care such as pain management, infection mitigation, and nutrition. This article describes oral pharmacologic agents intended to build new tissue and aid in wound healing, as well as an introduction to oral medications that interfere with wound healing. This review will not discuss the pharmacology of pain management or treatment of infection, nor will it address nutritional supplements.

KEYWORDS: drugs, oral medication, pharmacologic agents, wound healing

ADV SKIN WOUND CARE 2017;30:137–42.

INTRODUCTION

The art of wound care is as old as human civilization, and given the advanced medical science of recent decades, there is a surprising lack of oral medications that directly improve healing. The addition of an effective oral formulation to heal wounds would be immensely beneficial to the wound care field because of ease of use and acceleration of healing time. Of the oral medications available, most target ancillary aspects of wound care such as pain management, infection mitigation, and nutrition. There are several reasons for this, the first being the challenge of study design in patients with confounding factors that include multiple comorbid illnesses.[1] In addition, a wound healing treatment must meet the FDA requirement of full closure during a fixed investigational period with statistical significance.[2]

This review will not discuss the pharmacology of pain management or treatment of infection, nor will it address nutritional supplements including micronutrients. The scope of this article will include oral pharmacologic agents intended to build new tissue and an introduction to oral medications that interfere with wound healing.

ANABOLIC AGENTS

Optimum nutrition is a well-recognized component of wound healing.[3] Persons with wounds are often in a hypermetabolic or catabolic state. Pressure injuries, for example, commonly occur in debilitated patients with involuntary weight loss and protein-energy malnutrition. With a loss of 30% or more of lean body mass, the body will shunt resources from a wound to basic functions, essentially halting the healing process.[3] The same principles apply to wounds other than pressure injuries. A major strategy, therefore, has been directed toward development of anabolic medications intended to increase body weight and muscle mass.

There are 4 major anabolic hormones that potentially impact wound healing.[4] These include human growth hormone (HGH), insulin-like growth factor 1 (IGF-1), insulin, and testosterone and its analogs. Produced in the pituitary gland, HGH has powerful anabolic effects. These include accelerated cell proliferation, stimulation of IGF-1, and production and stimulation of uptake of amino acids into cells. Other metabolic activities of HGH include increased fat metabolism, increased protein and nucleic acid synthesis, increased insulin resistance, and decreased cortisol receptor activity. Although HGH has been shown to increase skin thickness in normal humans and increase the rate of re-epithelialization of skin graft donor sites, there is little or no data showing a positive impact on wound healing in humans.[4] Significant complications include increased insulin requirements, fluid retention, hypercalcemia, and increased metabolic rate. Finally, HGH is not available in oral form and must be administered parenterally.

Somatomedin C, another name for IGF-1, is similar in its physiologic effects to insulin.[4] It is produced in the liver, and its anabolic activity is directly related to HGH. It is recognized as a general wound healing stimulant and has fewer adverse effects than HGH, but its short half-life limits its clinical usefulness. Like HGH, it is not available in oral form.

Insulin is a hormone produced in the pancreas, which has anabolic activities in addition to its effect on glucose and fat metabolism. Clinical trials in burn patients have shown that insulin stimulates protein synthesis and increases net nitrogen uptake, but the effects on wound healing have not been well studied in humans.[4] In addition, insulin must be delivered parenterally.

Testosterone is a steroid hormone produced in the testes in men, and by the ovaries and adrenal glands in women, which has both masculinizing and anabolic properties. Even before the molecule was identified, topically administered testicular paste was considered a potential accelerator of wound healing.[5] Testosterone's anabolic properties include increasing skin thickness and muscle size and strength. Decreased production of testosterone is associated with increased age, injury, trauma, and chronic illness. Testosterone deficiency leads to catabolism and impaired healing, but exogenously delivered testosterone has not been demonstrated to have a positive direct effect on wound healing.[4]

Anabolic steroids are produced by modification of the testosterone molecule to decrease androgenic adverse effects while taking clinical advantage of its stimulation of protein synthesis and new tissue formation.[4] Oxandrolone is a synthetic derivative of testosterone with both anabolic and androgenic properties, and it is the only FDA-approved oral anabolic steroid for restoration of lost body weight. Adverse effects include cholestatic jaundice, increased risk of prostatic hypertrophy and cancer in men, and virilization in women.

In vitro and animal studies, as well as small therapeutic trials, showed that oxandrolone has positive effects on collagen synthesis, tensile strength, and bone and matrix formation. This led to great promise for wound healing, but orally administered oxandrolone has not met its once lofty expectations.[6] In one of the few major, randomized, placebo-controlled clinical trials with oral medication for pressure injuries, oxandrolone was tested in US Veterans Affairs' spinal cord units across the country.[7] The study was designed to test the efficacy of oxandrolone to heal chronic pressure injuries of the pelvic region that did not respond to standard or other treatment methods. Outcomes of the study were full closure of a pressure injury with proof of efficacy, as well as information on the rate of healing, and economic analysis on potential cost reduction. The investigators found no discernible evidence of facilitating wound healing or benefit in keeping a healed wound closed, with no more beneficial effect above the usual standard of care.[7]

OREXIGENIC MEDICATIONS

Given the close association of nutrition with the wound healing process, it makes sense that increased oral intake of nutrients and weight gain is beneficial.[8] Protein-energy malnutrition can result from either the catabolic state of acute illness or the cytokine-associated anorexia/cachexia syndrome often seen with aging and chronic illness. Nutritional strategies are therefore a critical component of a plan to heal wounds, with nutrient intake calculated to include consideration of both the stress response and the increased requirements of wound healing.[9] This includes protein, calories, amino acids, and micronutrients.

Whenever weight loss is noted, reversible causes should be considered with interventions aimed at provision of adequate protein and calories.[8] The differential diagnosis of weight loss includes the catabolic state associated with acute illness, cytokine-mediated cachexia, starvation, age-related loss of muscle mass, depression, malabsorption, and hyperthyroidism. If weight loss continues despite implementation of standard environmental and nutritional interventions, orexigenic drugs (appetite stimulants) should be considered.[10]

One of the most commonly used oral medications for appetite stimulation is megestrol acetate, a synthetic progestin originally used as therapy in women with breast cancer. Megestrol improves appetite and body weight in people with human immunodeficiency virus/AIDS, although the precise mechanisms for weight gain are not known.[9] Adverse effects include deep vein thrombosis (DVT), glucose intolerance, abdominal symptoms, and increase in low-density lipoprotein.

Dronabinol, a synthetic version of delta 9-tetrahydrocannibol, the active ingredient of marijuana, has been shown to be beneficial in patients with AIDS, cancer-related cachexia, and Alzheimer disease.[9] Adverse effects include drowsiness and confusion.

Other oral medications used for increased appetite and weight gain include mirtazapine, an antiserotonergic compound used for depression, and cyproheptadine, a first-generation antihistamine. Atypical antipsychotics including clozapine, olanzapine, risperidone, and quetiapine are also known to cause moderate weight gain but have not been recommended for cachexia or protein-energy malnutrition.[11] Evidence linking weight gain from orexigenic agents to improved wound healing is very limited.

HORMONE REPLACEMENT THERAPY

Estrogen can exert substantial influence on the physiology and composition of skin and may have a key role in maintaining skin integrity and structure. Several studies in both humans and animal models suggest that estrogen deprivation is a substantial factor in delayed wound healing.[12] Estrogen deficiency amplifies inflammatory responses and delays angiogenesis, whereas exogenous estrogen promotes re-epithelialization and matrix deposition by fibroblasts and increases local vascularization. Once popular for hormone replacement therapy in the perimenopausal years, the overuse of exogenous estrogens is in question.[12] Estrogen replacement has been associated with stroke, breast and total cancers, and DVT. Although theoretically beneficial for accelerated wound healing, oral estrogen replacement has not been recommended.

A new class of pharmaceuticals may hold promise for wound healing: the selective estrogen receptor modulators.[13] Examples include tamoxifen and raloxifene. These compounds exert tissue-specific agonist/antagonist activities that mimic estrogen effects while minimizing adverse effects. Their use in wound healing, however, remains to be investigated.[12]

ORAL MEDICATION FOR LOWER-EXTREMITY WOUNDS

The first step in formulating a treatment plan for lower-extremity wounds is to address the underlying illness and issues of diet and lifestyle. The diagnosis is critical for prescribing considerations, because a variety of diseases can lead to lower-extremity wounds including DVT, atherosclerotic disease, thrombophilic disorder, vasculitis, hemoglobinopathy, malignancy, hypertension, diabetes mellitus, hyperlipidemia, hypertension, and others. Vascular or podiatry consultations may be indicated for lower-extremity wounds. Once these steps are completed, oral medication can be considered.

Pharmacologic risk factor interventions for persons with atherosclerotic peripheral arterial disease include lipid-lowering therapy with statins and antihypertensive therapy. Treatment of diabetes mellitus must be individualized, balancing the deleterious

effects of elevated A_{1c} with the potential harms of hypoglycemia. Antithrombotic therapy, particularly antiplatelet monotherapy, with aspirin or clopidogrel has benefits in persons with symptomatic peripheral artery disease.[14] Cilostazol is an inhibitor of phosphodiesterase-3 that reduces platelet aggregation and enhances vasodilation and improves symptoms of claudication in patients with peripheral artery disease.[14] Although theoretically these antithrombotics can improve wound healing by improving circulation, there are few data to support routinely prescribing these medications for lower-extremity wounds.[14]

Pentoxifylline is a pharmaceutical with diverse properties. It is a theophylline derivative that is an antioxidant, vasodilator, and rheologic agent that increases erythrocyte flexibility and improves microcirculation and oxygen delivery.[15] Other effects include inhibition of inflammatory mediators, decreased cytokine release, and suppression of leukocyte function. There is a Cochrane review that recommends pentoxifylline for venous ulceration in combination with compression modalities to increase the chances of healing.[16]

COMPLEMENTARY APPROACHES

Complementary health approaches encompass a wide range of modalities with a history of use or origins outside conventional Western medicine. Examples are acupuncture, biofeedback, folk medicine, special diets, meditation, yoga, and many others. Recent decades have seen a significant increase in complementary modalities in all age groups in America.[17] However, the utility of complementary approaches, including nonvitamin, nonmineral, oral supplements for wound care, has not been well established.

Complementary approaches to cutaneous wound healing include phytotherapeutics (also known as ethnobotanicals) or plant-based medicines that have significant pharmacologic effects.[18] Numerous compounds have been described including aloe vera, mimosa, Echinacea, chamomile, ginseng, jojoba, tea tree oil, garlic, and ginkgo; however, all of these are administered topically.[18] Triphala is an ayurvedic herbal formula taken orally and recommended for numerous medicinal effects including wound healing, but scientific studies are limited.[19]

Another compound that has been reported for oral administration is curcumin. Curcumin (diferuloylmethane) is the major bioactive component of turmeric—a common spice used in South Asian countries in cooking and traditional medicine for centuries. A number of reports suggest that curcumin is a naturally occurring anti-inflammatory agent that has analgesic and prohealing effects on burns and other wounds.[20] Curcumin can be administered either topically or orally, but because of bioavailability issues, the optimum dosage and delivery route are still not established.

DRUGS THAT INTERFERE WITH WOUND HEALING

There are 4 commonly accepted phases of wound healing: coagulation, inflammation, proliferation, and wound closure with matrix remodeling and scar formation. Many growth factors and cytokines are involved, and each of these steps is vulnerable to disruption by specific oral medications.[21] Adverse effects can include delayed wound healing, wound dehiscence, and infection. Selected commonly used medications that interfere with wound healing are listed in the Table.

Coagulation, the earliest step, is mediated by platelet-derived growth factor, transforming growth factor, and other coagulation factors. Oral anticoagulants such as warfarin and the newer anticoagulants such as apixaban, rivaroxaban, and dabigatran can inhibit coagulation factor production. Antiplatelet medications such as aspirin, clopidogrel, and dipyridamole can inhibit the platelet's ability to clot. Cytotoxic agents such as methotrexate can directly destroy production of platelets. Any of these medications can potentially inhibit the early stages of wound healing.[21]

Nonsteroidal anti-inflammatory drugs are relatively inexpensive and often prescribed for pain control. Other medications in a similar class include selective cyclooxygenase 2 inhibitors such as

Table.
SELECTED ORAL MEDICATIONS THAT CAN INHIBIT WOUND HEALING

Medication	Class
Apixaban	Anticoagulant
Aspirin	Nonsteroidal anti-inflammatory drug
Azathioprine	Immunosuppressant
Capecitabine	Antimetabolite/chemotherapeutic
Celecoxib	Selective cyclooxygenase 2 inhibitor
Clopidogrel	Platelet aggregation inhibitor
Corticosteroids	Immunosuppressant
Cyclosporine	Immunosuppressant
Dabigatran	Anticoagulant
Dipyridamole	Platelet aggregation inhibitor
Ibuprofen	Nonsteroidal anti-inflammatory drug
Methotrexate	Antimetabolite
Mycophenolate	Immunosuppressant
Naproxen	Nonsteroidal anti-inflammatory drug
Rivaroxaban	Anticoagulant
Valdecoxib	Selective cyclooxygenase 2 inhibitor
Warfarin	Anticoagulant

celecoxib and valdecoxib. Their mechanism of action is inhibition of the inflammatory mediator prostaglandin E_2, the lipid mediator of inflammation in the wound healing process.[21] Animal studies have demonstrated an antiproliferative effect on blood vessels, delaying healing rates.[22] Because of the inhibition of inflammation that is a critical component of wound healing, nonsteroidal anti-inflammatory drugs and selective cyclooxygenase 2 inhibitors should be used with caution.[23]

Chemotherapeutic agents not only target rapidly dividing cancer cells, but also inhibit wound healing. Effects can include delayed inflammatory phase of healing, decreased fibrin deposition and collagen synthesis, and delayed wound contraction.[21] An example of an oral chemotherapeutic agent is capecitabine. Methotrexate is an oral chemotherapy agent and immunosuppressant that is used for treatment of malignancies, as well as autoimmune diseases. When prescribed for autoimmune disorders, methotrexate and azathioprine are sometimes classed together as disease-modifying antirheumatic drugs, and all have a potential negative impact on wound healing.[24]

Immunosuppressant drugs are a class of agents that reduce the body's immune system and are often prescribed to prevent organ rejection, to treat autoimmune diseases such as lupus, and other diseases such as psoriasis. Oral versions of these medications include cyclosporine, azathioprine, and mycophenolate. These medications interfere with T cells and other inflammatory mediators and can therefore impede wound healing. Dose reductions or avoidance of these drugs is recommended until complete wound healing occurs.[25]

Corticosteroids impact wound healing by stabilizing lysosomes within neutrophils, inducing anti-inflammatory proteins, and inhibiting cytokine release and chemotaxis.[24] Other effects include fibroblast dysfunction, reduced collagen production, angiogenesis, re-epithelialization, and decreased wound tensile strength.[24] Clinical consequences can be severe and include delayed wound healing, dehiscence, infection, and permanent weakening and atrophy of the skin. Other systemic complications of oral corticosteroids include drug-induced diabetes mellitus. There is some evidence that androstenediol can reverse the inhibitory effects of steroids on wound healing; however, corticosteroids should be avoided if possible in patients with healing wounds.[26]

SUMMARY

The historian Guido Majno[27] eloquently stated that the art of healing is one of humankind's greatest creations. In addition, the care of wounds is arguably the oldest of the healing arts. Given the scientific and technologic advances of recent years, it is therefore surprising that there are few oral medications that improve the healing of wounds. Wound healing research has been hampered not only by multiple comorbidities in persons with chronic wounds, but also by poorly defined outcomes and variables, lack of standardization in data collection, and variations in the definition, measurement, and treatment of wounds.[28] This article visited specific classes of oral medications offered to improve wound healing, albeit with limited efficacy. Many medications known to inhibit wound healing, on the other hand, are well recognized. An oral medication that accelerates wound closure would be a boon to mankind and would surely decrease healthcare expenditures. It is to be hoped that medical research will provide us with such a product in our lifetime.

PRACTICE PEARLS

- Oral pharmaceuticals that enhance wound healing—apart from pain management, infection control, and nutritional supplements—are few and far between.
- Oral anabolic steroids have shown limited effectiveness in wound healing.
- Oral orexigenic agents (appetite stimulants) include megestrol acetate, dronabinol, and others, but evidence linking these agents to improved wound healing is limited.
- Hormone replacement therapy, although theoretically beneficial, has not shown promise for accelerated wound healing.
- The only oral medication that has shown possible use for lower-extremity wounds is pentoxifylline for venous ulcers in combination with compression modalities.
- Many classes of oral medication can inhibit wound healing, including anticoagulants, nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, disease-modifying antirheumatic drugs, immunosuppressants, and corticosteroids.

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