CHAPTER **50**

AGENTS FOR WOUND CHEMOTHERAPY FOR VAC THERAPY AUGMENTATION: An Overview of Evidence

Nicholas A. Giovinco, DPM
David G. Armstrong, DPM, MD, PhD

INTRODUCTION

Chemotherapy is classically defined as the treatment of disease by use of chemicals. Traditionally, this is associated with the field of anti-neoplastic cancer therapy and infectious disease, but technically includes any such chemically-based treatment modality that heavily relies on a therapeutic index for justification. In addition to microbial management of a wound environment, this term has recently become adopted in the field of wound healing for several additional purposes. Exploration in this application has currently been achieved by utilizing topical and streaming means. With further evidence, this concept of wound chemotherapy will continue to mature. Wound chemotherapy is best seen as an enabling factor, which further extends the clinicians ability to manipulate a wound environment on a biochemical level.

The benefits of maintaining cleanliness, regular lavage, irrigation, and drainage of open wounds and compound fractures has long been appreciated in medicine. As the development of sterile and antiseptic protocols has progressed, several early efforts of wound installation have been implemented and documented in the medical literature dating back well over a century ago (1). In recent decades, the advent and application of negative pressure wound therapy (NPWT) has been further augmented with the instillation of chemotherapeutic agents (2). Notably, several such agents have been identified in early reports to show potentially promising results. In addition to this, several more suspected chemotherapeutic substances merit further investigation as well, specifically Carrel-Dakin hypochlorous acid, doxycycline, dilute betadine, lactoferrin, insulin, phenytoin, biguanide antiseptics, lidocaine, and diclofenac.

CARREL-DAKIN HYPOCHLOROUS ACID

Co-developed by Alexis Carrel and Henry Drysdale Dakins in Compiègne, France, this war effort invention was to serve a growing need for the septic conditions of combat injuries and open wounds incurred during the Great War. By combining saline, boric acid, and chloride bleach, this substance retained a stabilized acidic pH thus making it a therapeutically useful as a wound irrigation medium. Dakin's solution has demonstrated potential in NPWT constructs solely as well as in concert with other substances (3-5).

DOXYCYCLINE

Doxycycline is a semi-synthetic tetracycline compound. Classically, this drug is used in podiatry and wound care for its properties of antibiosis and antisepsis. There have, however, been some investigations of doxycycline and other chemically modified tetracycline species (CMTS), which demonstrate its potential as an inflammatory modulator within a wound environment (5,6). This is particularly so as an inhibitor of nitric oxide (NO) production, matrix metalloprotease (MMP) activity, and tissue necrosis factor alpha converting enzyme (TACE) (7).

The presence of NO within a wound environment is made possible by its production via the iNOS enzyme. The mRNA molecule, which codes for iNOS is expressed during times of cytokine and inflammatory stimulation. This mRNA molecule has a relatively short half life, which is presumed to be for regulatory purposes, and is stabilized by the presence of p38 MAPK binding to one of several 'AUUA' motifs (8). This stabilizing protein prevents the degradation of iNOS mRNA, which consequently permits the further expression and release of NO. Doxycycline prevents p38 MAPK from stabilizing iNOS mRNA, via competitive binding to metallic ions, and therefore acts to decrease the concentration of NO within the wound environment (9).

MMP activity has been identified as a key player in the environment of chronic wounds as well. Although MMPs are part of the normal breakdown and remodeling of tissues within the human body, nonhealing ulcers are particularly less governed by regulatory mechanisms and therefore see an overabundance of MMP activity, therefore leading to the persistence of inflammation and degradation of the epithelial matrix in situ. The chemical structure of doxycycline has been investigated, and demonstrated

satisfactory results as an inhibitor of such zinc catalyzed protease activity. Further studies have demonstrated the prevention of aortic aneurysms when doxycycline is taken systemically (10).

Similar to MMP inhibition, TACE (otherwise known as ADAM17) inhibition works by zinc binding as well. As members of the same metalloprotease superfamily, TACE degrades pre-TNF-a, thus converting it to a biologically active form. Because TNF-a has long been known as a powerful member of the entourage of inflammatory cytokines of chronic wounds, the ability to suppress its expression could potentially be to the patient's advantage. Doxycycline has demonstrated convincing results in lowering the conversion of pre-TNF-a to its active form (11).

DILUTE BETADINE AND OTHER IODINE SPECIES

Betadine and other iodine containing solutions are well known for their usefulness in establishing sterility and antiseptic prophylaxis. Highly concentrated forms of betadine are typically discouraged in an open wound environment and are considered to be causative in necrosis and decreased tissue healing. In some studies, dilute concentrations of betadine have demonstrated less tissue toxicity, while still retaining many of the prophylactic and therapeutic advantages (12). This could potentially be a therapeutically useful agent when instilled through NPWT foam dressings.

LACTOFERRIN

Lactoferrin (lactotransferrin) is a naturally occurring protein within the human body, and has a high affinity for binding iron (Fe+3). Because bacteria, viruses, and leukocytes all utilize iron for cell binding and migration, the infusion of lactoferrin as well as other recombinant derivatives is potentially useful on a biochemical level (13). Laboratory and clinical studies of lactoferrin have confirmed its effectiveness, not only as an antimicrobial and antiviral substance, but also as an immune modulator. By this, the overall inflammatory processes commonly exhibited by chronic wounds could be better maintained and modulated (14).

INSULIN

Insulin is a powerful growth hormone to a plethora of various anabolic and regulatory pathways within the human body. Many of these pathways are associated with systemic diabetic complications. Conversely, there are several applications of insulin and other growth factors, when applied locally via topical or streaming means, could prove to be beneficial to diabetic foot complications (15). This is attributable to the antidegrative properties that such growth hormones have on tissue matrices and proliferative activity.

PHENYTOIN

Phenytoin is classically used in the treatment of epilepsy and other neurological disorders. Systemic and topical applications of phenytoin have been studied and revealed intriguing evidence as to its usefulness in treating chronic wounds (16,17). The presence of phenytoin in a healing environment has demonstrated an ability to increase fibroblast activity and is overall inductive to the proliferation and formation of granular wound beds (18). There are many side effects associated with the use of phenytoin. Because many of these effects are a result of systemic administration of phenytoin, whereby topical application of phenytoin stands to circumvent many of the adverse pathways (19).

BIGUANIDE ANTISEPSIS

Chlorhexadine is a powerful antiseptic, which is utilized in a variety of surgical and hospital settings. Its broad spectrum effectiveness against gram positive, gram negative, and viral bodies has been established with relatively few exceptions.These chemicals are typically safe enough for bodily and oral use, and is a common active ingredient in mouth wash. Given the presence of biofilm and bacterial colonization within the human oral cavity, chlorhexadine instillation could prove to be a useful substance in the chemotherapeutic arsenal of wound care specialists (20).

LIDOCAINE

Dressing changes with NPWT can often be a painful experience for patients without significant neuropathy. For this, several techniques have been developed to mitigate the painful growth and adherence of epithelialization to NPWT dressings in wound beds (21). Lidocaine is a widely popular analgesic utilized in podiatric medicine. Topical application of lidocaine is commonly used in dermatoloic procedures and burn wound patient care. The instillation or infusion of lidocaine into wound dressings prior to dressing changes has demonstrated a reduction in the typical discomfort experienced by the removal and application of NPWT foam dressings, in non-neuropathic patients (22, 23).

DICLOFENAC

Diclofenac is a powerful anti-inflammatory and analgesic component of the NSAID family. In addition to these properties, diclofenac is also being investigated for its antibiotic properties against e. coli and salmonella, which are two organisms commonly cultured in lower extremity wounds (24). Diclofenac can be utilized through both systemic and topical routes. Similarly to previously mentioned agents, diclofenac is associated with less potential for side effects when applied in a topical form.

CONCLUSION

Wounds and chronic ulcerations remain a challenging component of diabetic foot care. The presence of such complications place the patient into a perilous condition, which could last several weeks to months before closure is achieved. Offloading measures, which reduce peak plantar pressure are possibly the most important primary effort by the clinician, but the ability to exact maintenance and manipulation of the biochemical wound environment could prove to be a welcome improvement.

One notable observation about the use of vacuum foam dressings with infusion ports, both modified as well as designed, is the increased reliance on patient compliance. This is seen, more so, with the use of such chemovac devices outside of hospital and specialized care facilities, where strict adherence to therapeutic instructions and foam dressing application is not always satisfied. In this event, the discontinuation of chemovac therapy may need to be considered, in favor of standard dressings or NPWT.

Instillation and topical applications of chemical agents are not new to the science of wound healing. The concept of wound chemotherapy is merely part of the growing knowledge and ability to utilize these various substances to achieve a diverse means. Negative pressure wound therapy and other such vacuum assisted closure devices, when used alone, have proven successful results in a variety of challenging wounds. When augmenting the management of diabetic foot complications with the NPWT and/or chemotherapeutic agents, the influence of care providers could be further extended.

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