Expert Opinion

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The use of gentamicin-impregnated foam in the management of diabetic foot infections: a promising delivery system?

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Diabetic foot ulcers are frequently complicated by infection due to increased bacterial load. Antimicrobial therapy is an important component of the management of these wounds; however, to be effective, the therapy must provide adequate tissue concentration of an appropriate antimicrobial agent at the target site. Thus, drug concentrations in the interstitial space are an important determinant of successful therapy. Gentamicin sulfate has been proven to be active *in vitro* against many strains of Gram-negative and Gram-positive pathogens, yet it is often overlooked as a treatment option owing to toxicity risks associated with parenteral delivery. The incorporation of this agent into a collagen-gentamicin implant allows physicians to limit risk by providing a controlled dose of the drug to the target site. This decreased level of risk, combined with the fact that the implant is biocompatible and does not require removal, makes the gentamicin-collagen implant a superior drug delivery system.

Keywords: aminoglycocides, biofilm, collagen, diabetes mellitus, diabetic foot wounds, gentamicin sulfate, Gram-negative infection, Gram-positive infection

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1. Introduction

Diabetic foot ulcers are frequently complicated by infection, with an average of 10% of people with diabetes requiring antibiotics every year [1-6]. Antimicrobial therapy is an important component in the management of these wounds because increased bacterial loading has been linked to an overall reduction in healing rates [7]. Infecting bacteria produce a range of toxins and enzymes that serve to promote spread within the human tissues. Furthermore, these bacterially produced enzymes and toxins compromise the patient's mechanical and cellular defences, thus providing a more favorable local environment for bacterial growth. Effective antimicrobial therapy requires adequate tissue concentration of an appropriate antimicrobial agent to be delivered to the target site and thus drug concentrations in the interstitial space are an important determinant of successful therapy [8]. Successful antimicrobial therapy requires bioactive tissue concentrations that exceed the minimum bactericidal concentrations (MBCs) for infecting pathogen(s).

Also, the formation of wound biofilm represents an extra hurdle for the patient's defenses. Biofilms are a community of microorganisms encased within an extracellular polymeric matrix, which accumulates at a surface [8]. The bacteria resident within biofilms are less susceptible to the body's immune defense system

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as biofilm matrices have been shown to inhibit chemotaxis and other key immune function [9,10]. In fact, bacteria within biofilms may be up to 1000 times more resistant to antimicrobial agents than those in a planktonic state, for reasons yet to be fully elucidated [12].

Although much of the current research relating to the role of biofilms is directed at cutaneous wounds, there is ample evidence to demonstrate that a biofilms are implicated in a wide range of infective processes, including deep wounds and osteomyelitis [13]. Antimicrobial therapy optimized to deliver MBCs for infecting pathogen(s) may improve the chance of rapid bacterial eradication, thus avoiding the risk of biofilm formation. In light of the reduced susceptibility of microbes within the biofilm environment to antimicrobial therapy, modalities that deliver the highest local tissue concentrations while minimizing plasma concentrations would appear to offer the best chance of therapeutic success where other measures to disrupt the biofilm cannot be used.

2. Drug delivery

Antibiotics are typically administered orally, parenterally or topically. Although convenient for the patient and practitioner, oral administration of antimicrobial agents can be associated with significant variation in plasma concentrations and thus overall tissue bioavailability. Following absorption from the gut, the drug enters the hepatic portal system by means of the portal vein. As a result of this action, a proportion of the drug is metabolized by the liver before entry to the systemic circulation. This 'first pass effect' thus reduces the bioavailability of the drug and can impose significant variation on plasma concentrations.

Other routes of administration avoid the 'first pass effect' because they allow the drug to be directly absorbed into the systemic circulation. These include suppository, intravenous, intramuscular and sublingual routes of administration. Despite the potential to circumvent the 'first pass effect', there remains a wide range of other factors that may lead to variation in tissue concentration at a given target site. Pharmacokinetic and pharmacodynamic factors are extra sources of this potential variation.

Furthermore, drug interactions may serve to increase or decrease plasma concentrations owing to altered binding of drug, which thus serves to alter bioavailability. This in turn may impede drug efficacy and increase the likelihood of adverse effects.

Disease states such as diabetes mellitus have demonstrated reduced tissue concentrations of antibiotics compared with controls [14]. Impairment of microcirculatory function has been speculated to contribute to this reduced penetration of drug from the circulation to the tissues, that is, plasma to tissue concentration. Failure to achieve adequate tissue concentrations, that is, less than the MBC, risks both failure to resolve infection and the development of resistant microbial strains.

A further confounding factor is the ability of the circulatory system to deliver the drug to the target site. Impaired perfusion of the lower extremity due to macrovascular disease will result in substantially diminished tissue concentrations.

In addition to the potential compromising of the major transport system (i.e., arterial tree), bone and soft tissue infections are usually accompanied by the presence of localized barriers to antibiotic delivery. This places further limitations on the amount of drug that can be carried to the infection site through the blood vessels at a local level [15].

3. Diabetic foot wound and antibiotic selection

Diabetes mellitus is associated with dysfunction across a range of cellular, vascular and physicochemical processes, many of which adversely influence wound healing, and increase susceptibility for and the response to infection. Diabetic extremity ulcers are associated with chronic infections that are often polymicrobial in nature [3-6].

Gentamicin sulfate is a water-soluble aminoglycoside antibiotic that has been proven to be active *in vitro* against many strains of Gram-negative and Gram-positive pathogens (i.e., *Staphlococcus aureus*, *Staphylococcus epidermis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Enterobacter aerogenes*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria gonorrhoea*, *Pseudomonas aeruginosa* and *Serratia marcescens*). As Gram-negative anerobes are among the most common bacteria found in necrotic and ischemic wounds, it would stand to reason that gentamicin would be a powerful weapon against bone and soft tissue infections. After intramuscular administration, peak plasma concentrations are reached in 30 – 90 min. A dose of 1 mg/kg produces average peak plasma concentration of ~ 4 μg/ml, although there may be considerable inter-individual variation and higher concentrations in patients with renal impairment, the elderly and certain concurrent drug administration [15]. As a consequence of concerns over toxicity, gentamicin is often overlooked as a treatment option because of its risk of systemic toxicity, which may encourage the provision of either a more expensive or a less effective antimicrobial [15,16].

4. Gentamicin toxicity

Unfortunately, in order to overcome the aforementioned limitations, many physicians opt merely to increase the concentration of an antibiotic rather than consider an alternative dosing methodology. This practice in turn limits the number of antibiotics physicians have to choose from because aminoglycocides and other similar types of antibiotic have a high risk of ototoxicity and nephrotoxicity.

Ototoxicity occurs in 5 – 10% of patients receiving intravenous administration and probably relates to total dose given rather than simply a short period of high dose. It appears that both the daily dose and duration of therapy are

relevant to toxicity [17]. Concurrent administration of potentiating medications (e.g., furosemide, vancomycin) and genetic susceptibility may also play a part in the development of gentamicin toxicity [18]. Therefore, if a physician is committed to prescribing only systemic treatment, they may in fact choose a less effective antibiotic for treating bone and soft tissue infections in favor of a decreased risk of systemic complications. The error in this logic lies in the fact that studies have shown locally administered antibiotics are just as effective, if not more so, as their systemic counterparts, and often have a lower incidence of complication.

5. Summary

Antimicrobial therapy relies on adequate tissue concentrations of an appropriate drug to reach the target site predictably. Most routes of administration are susceptible to variation of peak plasma concentrations, which are particularly relevant to those with co-morbidities. Furthermore, delivery to the target site relies on a functional circulatory system. Topical administration using a biocompatible carrier affords accurate delivery while minimizing the risks of systemic complications. The collagen-gentamicin implant may represent a safe and economic means of delivering gentamicin directly to the site of infection with minimal risks of systemic toxicity.

6. Expert opinion

Topical antimicrobial therapy in the management of infected foot ulcers has been supported by several authors [19-21]. Gentamicin is most effective when delivered locally, as it delivers a higher concentration of drug without increasing the risk of morbidity. Pharmacokinetic studies have reported that local administration of gentamicin results in a higher concentration of the drug in excreted wound fluid. Investigators often found concentration levels that far exceeded the MBC levels for several bacteria up to 48 h post dosing (including those bacteria previously thought to be gentamicin-resistant) [15]. In addition, although the MBC levels were high in the wound bed itself, the gentamicin serum and urine levels were much lower than the toxicity threshold for aminoglycosides. Gentamicin is now available for use in intramuscular and intravenous injection, in antibiotic impregnated beads, and in a sponge-like collagen-gentamicin implant. Although all three of these modalities present a viable treatment option for bone and soft tissue infections, European studies have shown the collagen-gentamicin implant has to be the superior delivery mechanism.

Historically, local administration has been by means of antibiotic-impregnated polymethyl methacrylate (PMMA) beads. Although these beads are often impregnated with gentamicin, they are not the ideal choice for local administration. The beads act only as a carrier for the antibiotic and do not add anything unique to the treatment process. In addition, the beads must be removed during follow-up, which requires the patient to undergo a second surgical procedure, with both economic implications and the associated risks of a second procedure.

The collagen-gentamicin implant, on the other hand, is biocompatible and does not require the patient to incur the risk of further procedures. The device is therefore both economically and clinically superior. It measures $10 \times 10 \times 0.5$ cm and contains 130 mg of gentamicin sulfate and type 1 bovine collagen. The collagen used in the implant is similar to the collagen that occurs naturally in the human body, making up 95% of the osteoid organic matrix of bone and serving as a main component in cartilage and other connective tissues [16]. As collagen is broken down by collagenase as part of the body's natural process of collagen turnover, the implant does not have to be surgically removed, making it less risky for the patient.

In addition, although the collagen in the implant acts as a delivery vehicle for the gentamicin, it also aids in the body's own healing process. Owing to its hemostatic effect in wound beds, collagen provides an added benefit when treating chronic and postoperative wounds. Studies have shown that collagen interacts with platelets and fibroblasts to produce positive influence on wound healing [16]. In bone, osteoblasts are attracted to the wound site and stimulated to proliferate. The formation of osteogenic cells stimulates mineralization and the production of collagenous callus tissue to form new bone [16].

The implant has numerous advantages and is very versatile in its usability. The sponge-like material is flexible and can easily be manipulated and cut into small pieces and applied loosely to bone and soft tissue cavities.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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