PHMB and its potential contribution to wound management

In spring 2010, a multidisciplinary group of clinicians met in London to discuss the issue of bacterial management in wound healing. The clinical world is currently facing a range of new challenges and health care is becoming increasingly intensive with ever-higher expectations of positive outcomes from both the healthcare industry and those it serves. As our understanding of the intricate balance between wound healing and the bio-community of organisms living within the wound expands, clinicians face new challenges in providing effective strategies to manage wound bioburden without inducing pathogen resistance and negatively influencing the healing process.

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The emergence of bacterial strains resistant to the components of a number of antimicrobial preparations has led to major concerns that a new threat to wound care is emerging.

A multidisciplinary group of clinicians comprising microbiologists, tissue viability consultants and specialists, orthopaedic, reconstructive and general surgeons and academics in wound care (*Box 1*), held a consensus meeting in the spring of this year to discuss the issues for clinicians in the 21st century; where is the evidence, and how can clinicians ensure that the use of antimicrobials is carefully managed to maintain clinical effectiveness and ensure appropriate use of healthcare resources?

All authors were members of the consensus meeting panel; * Chair of the panel. Full author details in Box 1

With a lack of new antibiotic therapies emerging on the horizon, the role of topical antiseptic/antimicrobial agents may take on an even greater significance. One possible solution lays with polyhexamethylene biguanide (also known as polihexanide or PHMB), a compound which has been available for around 60 years in a number of formats, but which has only recently entered the UK wound care market.

It was agreed at the multidisciplinary meeting that judicious introduction and use of this antimicrobial agent could offer UK clinicians another weapon in the fight for bacterial control. The document resulting from the meeting, provides a framework for clinical utilisation of this technology (*PHMB and its potential contribution to wound management*, 2010, available online at: www.wounds-uk.com/downloads/phmb_consensus_document.pdf). The document aims to educate and inform clinicians and provide industry with key performance indicators for future product development.

The problem of bioburden

The influence of bacteria on wound healing is complex and controversial. It is accepted that most open, chronic wounds are colonised with bacteria, and yet most wounds, even chronic wounds, can and do heal. Wound infection is the result of a complex interaction between the individual's immune system, the wound conditions and the numbers and virulence of the bacteria present (Dowsett et al, 2004; Best Practice Statement, 2010).

Chronic wounds are often heavily colonised with bacteria or fungal organisms. This is partly due to remaining open for prolonged periods of time, and also to underlying medical problems such as poor blood supply, hypoxia and metabolic disorders (Hunt and Hopf, 1997; Ovington and Eisenbud, 2004). Wound infection can result in enlargement of the wound, the need for surgical intervention (even amputation), and may even lead to life-threatening events (Gethin, 2009; Landis et al, 2007). Localised, often sub-clinical infection is recognised as a major factor in prolonged wound healing, and its effective management and treatment is identified as a central tenet when undertaking Wound Bed Preparation (WBP) (Schultz et al, 2003).

Wound-acquired systemic infection is one end of a broad spectrum of bacterial influence on the wound extending from simple bacterial contamination. This 'continuum of infection' (Kingsley, 2001; White et al, 2001) represents not only the establishment and proliferation

BOX 1

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of bacterial communities within the wound, but the ability of the host to mount a successful immune response to pathogenic ingress.

If host defences are strong, bacterial proliferation is halted and the wound progresses to healing. However, if defences are weak or pathogenic, virulence is high, bacterial proliferation continues, wound repair is halted and eventually systemic sepsis occurs.

It is recognised that single species communities of bacteria are rare in nature (Cooper and Okhiria, 2008). Instead, bacteria exist in diverse communities, which on occasion will include fungi and viruses. Recently, there have been discussions about the possibility of biofilm development within wounds. Biofilms are communities of organisms living within a three-dimensional extracellular polysaccharide matrix (Phillips et al, 2010). The formation of these bacterial communities is well established in industrial and dental research, where biofilms are routinely studied and engineered. However, in the field of wound care, although they seem to be a key component in resistant bacterial colonisation (Serralta et al 2001), our understanding of biofilms and their effect on wound healing is limited. It certainly appears that chronic wounds provide an environment capable of supporting the development of bacterial biofilms. Further research is needed before it can be conclusively stated that biofilms are a threat to the wound healing process.

Managing wound bioburden

The presence of bacteria in acute or chronic wounds does not necessarily indicate that infection has occurred, or that it will lead to impaired wound healing (Kerstein, 1997; Dow et al, 1999). As new information is presented, many clinicians believe that high levels of bacteria may inhibit healing in the absence of traditional signs of infection (Edwards and Harding, 2004; Warriner and Burrell, 2005). The equilibrium in the wound is tipped in favour of the bioburden (i.e. the colonising bacteria are negatively impacting the healing potential of the wound), and active intervention is indicated.

The presence of spreading infection has potential serious implications for patient well-being and appropriate systemic antibiotic therapy should be considered (European Wound Management Association [EWMA], 2006; World Union of Wound Healing Societies [WUWHS], 2008). The clinical diagnosis of wound infection was described by Cutting and Harding (2004) as:

- Redness (erythema)
- Swelling (oedema)
- Localised heat
- Pain
- Limited function.

However, they expanded on this traditional view by stating the following parameters should also be considered:

- Delayed healing
- Wound breakdown
- Pocketing at the base of the wound
- Epithelial bridging
- Unexpected pain or tenderness
- Friable granulation tissue
- Discolouration of the wound bed
- Abscess formation.

This has been further refined within the WUWHS document (2008) to take into account the subtle differences in presentation that are observed between acute and chronic wounds of different aetiologies.

The usefulness and significance of wound swabbing in the context of wound infection is still a subject of controversy. While a microbiological examination is indicated in the presence of classic signs of infection, the results of these tests need to be considered within the context of a full clinical assessment before they are considered a factor in therapeutic decision-making. It must be remembered that generally, systemic

antibiotics are not recommended for wounds that only show signs of local infection (Bowler et al, 2001; Sibbald, 2003; EWMA, 2006; WUWHS, 2008), a state referred to as 'critical colonisation', 'covert' or 'occult infection'. In addition, topical antibiotics are linked to the development of bacterial resistance, and thus should be avoided.

However, in the colonised and critically colonised state, topical antiseptic/antimicrobial agents have been shown to play a significant role in reducing bacterial load (EWMA, 2006). Topical antiseptic/antimicrobial agents represent the first line of treatment in the management of bacterial burden, as they provide a high antimicrobial concentration at the site of infection (White et al, 2001; Cooper, 2004) and some have bactericidal effects against multi-resistant organisms such as meticillin-resistant *Staphylococcus aureus* (MRSA) (Lawrence, 1998; Sibbald et al, 2001). Topical antiseptic/antimicrobial agents have the additional advantage that they do not interfere with the protective bacterial flora in other parts of the body, and are also less likely to produce an allergic reaction.

It is important that the use of antimicrobial measures is targeted at those with an assessed significant bioburden, or those with a severely compromised host defence mechanism. Widespread, inappropriate use increases healthcare costs with no outcome gain. Guidance for the safe and effective use of topical antiseptic/antimicrobial agents can be found in the 2010 Best Practice Statement, *The use of topical antiseptic/antimicrobial agents in wound management.* In summary:

- Topical antiseptic/antimicrobial preparations are indicated for: the treatment of individuals with colonised wounds where the patient is immunocompromised; for critically colonised wounds; for locally infected wounds; and as an adjunct in the management of systemic wound-based infection
- The use of topical antiseptic/antimicrobial agents should be targeted to those with, or at risk of high bacterial wound bioburden
- The use of topical antiseptic/antimicrobial agents should be time-limited: if no wound response is seen after 10 days of use, an alternative topical antimicrobial agent should be initiated or systemic antibiotics should be considered; if wound improvement is observed, antimicrobial therapy should be discontinued if no longer considered appropriate. No treatment should extend beyond 14 days without discussion with a local specialist unless previously agreed or indicated by clinical need
- The form of product used should reflect the clinical needs of the individual. This will include the need to manage wound exudate and minimise wound trauma on removal.

Polyhexamethylene biguanide (PHMB)

The antiseptic/antimicrobial compound PHMB is a synthetic polymer structurally similar to naturally occurring antimicrobial peptides (AMPs). The basic molecular chain of PHMB can be repeated from 2–30 times, with increasing polymer chain length correlating with increasing antimicrobial efficacy.

The structural similarities between AMPs and PHMB mean that the latter can enter bacterial cell membranes and kill bacteria in a similar way to AMPs (Moore and Gray, 2007). The primary targets appear to be the outer and cytoplasmic membranes. PHMB is thought to adhere to and disrupt target cell membranes, causing them to leak potassium ions and other cytosolic components (Davies et al, 1968; Davies and Field, 1969; Broxton et al, 1984; Yasuda et al, 2003), which results in bacterial cell death. There is also evidence that following penetration into target cells, PHMB binds to DNA and other nucleic acids (Allen et al, 2004), damaging or inactivating bacterial DNA.

Efficacy

Antimicrobial activity is a key performance indicator of any product used in treating and managing bioburden. PHMB has a number of properties and characteristics which make it particularly appropriate for use in critically colonised and locally infected acute and chronic wounds. These can be summarised as:

- Proven broad antimicrobial action (Cazzaniga et al, 2002; Wright et al, 2003; Eberlein and Wild, 2007; Mosti et al, 2008; Müller and Kramer, 2008; Mueller and Krebsbach, 2008; Kaehn, 2009; Wild et al, 2009)
- Antifungal activity (Shah, 2000; Lee et al, 2004)
- Minimum blood/protein inactivation (reduction of effect on mucous membranes due to presence of mucin) (Ansorg et al, 2002)
- Sustained post-application effect (Rosin et al, 2002)
- Established promotion of wound healing (depending on concentration) (Davies and Field, 1969; Kramer et al, 2004; Daeschlein et al, 2007; Wiegand et al, 2008)
- Additional anti-inflammatory properties
- No development of resistance reported to date (Gilliver, 2009; Wiegand et al, 2009)
- Reduction of biofilm (Harbs and Siebert, 2007) and fibrin (Körber et al, 2008).

Safety

PHMB has been in general use for approximately 60 years with no evidence of the development of resistance (Moore and Gray, 2007). It exerts little toxicity and has been found safe and effective in applications as diverse as treatment of eye infections and sanitising swimming pools (Larkin et al, 1992; Motta, 2004; Motta and Trigilia, 2005). Specifically, studies in 1998 and 2005 (total of 3,529 patients) have shown that skin sensitising to PHMB is low (approximately 0.5%), even though the tested drug concentrations (2.5 and 5%) were five to ten times the concentration normally used in wound applications (Schnuch et al 2000; 2007). Comparative tests of PHMB's biocompatibility (measurement of an antiseptic/antimicrobial agent's activity in relation to its cytotoxicity) against other commonly used therapies have demonstrated its superiority to chlorhexidine, povidone-iodine, triclosan, silver and sulfadiazine (Müller and Kramer 2008).

In summary, PHMB has:

- Good clinical safety (Disch et al, 2007; Mulder et al, 2007; Bruckner et al, 2008)

- Targeted action on bacterial cells (specific mechanism of action with regard to acidic lipids of bacterial membranes, with only minor effects on neutral lipids of human cellular membranes) (Ikeda et al, 1983; 1984)
- Biocompatibility index >1 (Müller and Kramer, 2008)
- No known risks of resorption (Kramer and Roth, 2008)
- No known toxic risks (Moore and Gray, 2007)
- Low risk of contact sensitisation (Schnuch et al, 2000; 2007)
- Sustainability of the active pharmaceutical ingredient (Lee et al, 2004).

Wound management products containing PHMB

PHMB can be effectively delivered to the wound in a number of formats. The choice of presentation depends on the objective of treatment and product availability.

Antiseptic/antimicrobial solutions (medicinal products)

At present there are no commercially available PHMB antiseptic/antimicrobial solutions available on the UK Drug Tariff. In Europe, Serasept® (Serag-Wiesner KG) is the only PHMB solution available as an approved finished drug product with antiseptic/antimicrobial effects. Antiseptic/antimicrobial solutions can be made up by pharmaceutical departments from commercially available raw materials. Antiseptic solutions can be made up by approved, licensed, pharmaceutical manufacturing departments on an individual named-patient basis from commercially available raw materials. Reference sources suggest in these circumstances PHMB solutions are used at concentrations of 0.01%, 0.02%, or 0.04% (Dissemond et al, 2010). As PHMB has an initial slow onset of action, and different pathogens respond to the agent with different exposure times, it is important to allow a minimum exposure time of 10–15 minutes after the wound base has been thoroughly wetted (Werner and Kramer, 1995). In Europe the following guidelines for use are given (Dissemond et al, 2010):

- Acute, contaminated, severely purulent wounds: use a 0.04% solution
- Clinically infected chronic wounds: use a 0.04% solution
- For application in suction/rinse drainage: use a 0.02% solution
- Intra-operative wound contamination: use a 0.01% solution for decontamination
- Colonised chronic wounds (particularly in 'at risk' groups): use a 0.01–0.02% solution.

Wound rinsing solutions (medical devices)

The wound rinsing solution Prontosan® (B Braun Medical Ltd, Sheffield, UK) is not considered to be an antiseptic/antimicrobial agent, but a medical device with PHMB added as a preservative, i.e. the company product claims are based on a purely physical cleansing effect.

Antiseptic/antimicrobial gel preparations (medicinal products)

At present no antiseptic/antimicrobial gel preparations are commercially available in the UK. In Europe, products are manufacturerd by pharmacy departments for the prophylaxis and therapy of infected wounds (Dissemond et al, 2010). The common recommendation for infections with Gram-negative pathogens is to use the higher concentration (0.1%) (Dissemond et al, 2010).

Wound dressings containing PHMB (medical devices)

The wound dressing products Telfa® AMD and Telfa AMD Island (Covidien UK Commercial Ltd, Hampshire, UK) are constructed as low absorbency perforated plastic film-faced wound dressings impregnated with PHMB, and are marketed as a barrier to bacterial colonisation. Kendall AMD, Kendall AMD Plus (Covidien UK Commercial Ltd, Hampshire, UK) are constructed as a foam-based dressing containing PHMB. It is claimed that these products can act as an effective antimicrobial barrier and can reduce bacterial load within wound exudate. All of these products are currently listed on the UK Drug Tariff as antimicrobial dressings.

Suprasorb® X+PHMB (Activa Healthcare, an L&R Company) is a biosynthetic cellulose fibre dressing impregnated with PHMB. It is claimed by the manufacturer that this product is able to donate PHMB at the wound surface and into the wound fluid, making it an effective treatment for infected and colonised wounds. Suprasorb X+PHMB is currently listed on the UK Drug Tariff as an antimicrobial dressing.

Contraindications

PHMB must not be used (Deutscher Arzneimittel Codex, 2008):

- For peritoneal lavage
- For antiseptic joint lavage (cartilage toxicity)
- In applications involving any part of the central nervous system (CNS), including the meninges and intralumbal applications
- For applications involving the middle or inner ear, or for intraocular applications
- During the first four months of pregnancy (at any time thereafter, a strict benefit/risk assessment has to be performed)
- In patients allergic to PHMB.

Topical treatment approach with PHMB and other therapeutic procedures

The use of topical antiseptic/antimicrobial agents (including PHMB) has been shown to assist the management of bacterial burden within the wound environment. However, the use of these products needs to be undertaken as part of a structured approach to wound management, as indicated within conceptual frameworks such as WBP (Kingsley, 2001; White et al, 2001; EWMA, 2004). The decision to use a specific antiseptic/antimicrobial agent must be measured against product availability, antimicrobial efficacy, wound toxicity, systemic absorption and the potential for development of bacterial resistance.

PHMB is available in a number of wound care formats (i.e. irrigation fluid, gauze and foam-impregnated dressings), which, due to their specific modes of action, are able to manage bioburden by either preventing the ingress of bacteria into the wound, or delivering a potent antiseptic/antimicrobial agent to the wound bed. PHMB-based products have proven broad antimicrobial spectrum and good cell and tissue compatibility. PHMB has a low risk of contact sensitisation, has no conclusive evidence of pathogens developing resistance and PHMB-based products have been proven *in vitro* and *in vivo* to promote wound healing.

PHMB offers wound care an alternative approach to the issue of bioburden management; one which can easily be incorporated into current wound infection treatment and prevention regimens. Further work is needed to produce a range of PHMB-based products which can provide wound-appropriate methods of delivering the beneficial effects of this compound to our clients.

Conclusion

The development of bacterial resistance to certain antimicrobial products and recent concern over systemic absorption and accumulation of silver has prompted a reappraisal of the antiseptic/antimicrobial measures that clinicians can safely utilise in managing bacterial burden. Used appropriately, PHMB is a highly effective and safe antiseptic/antimicrobial agent which can be an efficacious alternative to silver and iodine-based antiseptic/antimicrobial wound care products. As clinicians, we need to ensure the judicial use of this product, and that manufacturers deliver PHMB-based products that are tailored to meet our requirements and the needs of our patients. WUK

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Key points

- A multidisciplinary group of clinicians met in London to discuss the issue of bacterial management in wound healing.
- Use of antiseptic/antimicrobial measures should be targeted at those with an assessed significant bioburden, or those with a severely compromised host defence mechanism.
- PHMB is an effective and safe antiseptic/antimicrobial agent which can be an efficacious alternative to silver and iodine-based antimicrobial wound care products.

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