Octenidine: antimicrobial activity and clinical efficacy

This review summarises the microbiological activity and clinical efficacy of octenidine, a broad-spectrum antimicrobial that is currently available as a gel and irrigation solution for wound care, as well as a body wash for decolonisation. The review considers the experimental and clinical evidence showing that octenidine-containing products improve outcomes across a range of settings including burns, pressure and leg ulcers, without compromising wound healing or producing clinically significant cytotoxicity. Furthermore, decolonisation with octenisan® wash lotion could reduce pathogen carriage from the community into hospital, facilitating infection control.

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Irrigation solution

Concerted efforts by healthcare professionals and heightened public awareness has reduced the incidence of hospital-acquired infections in recent years. For example, the number of reports of meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in England declined by 52% between January and March 2009, and January and March 2011. Similarly, the number of *Clostridium difficile* infections declined by 65% between the quarterly average during 2007/8 and January to March 2011 (Health Protection Agency [HPA], 2011). Nevertheless, English trusts reported 334 and 4827 cases of MRSA bacteraemia and *Clotridium difficile* infection respectively between January and March 2011 (HPA, 2011). Clearly, healthcare professionals, and society more generally, cannot yet lower their bacteriological guards.

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Against this background, products containing octenidine, an effective and well-tolerated broad-spectrum antimicrobial agent, have helped healthcare professionals manage hospital-acquired infections and improve wound care. First launched in the UK during 1990, octenidine is available in three formulations in the UK: octenilin® wound gel (0.05% octenidine); octenilin® wound irrigation solution (0.05% octenidine); and octenisan® wash lotion (0.3% octenidine) for decolonisation. All three products are available on the Drug Tariff and octenisan wash lotionis also available over-the-counter from pharmacists. This paper, funded by Schülke UK, summarises the microbiological activity and clinical efficacy of this product for infection control and wound care.

Microbiological activity

Wounds readily support bacterial growth (Kirker, 2009), which can transform relatively sterile superficial damage into difficult-to-treat infected chronic wounds. Two key factors drive this transformation. Firstly, biofilms — clusters of cells encased in a protective matrix of polysaccharide polymers secreted by bacteria (Kirker, 2009; Werthén et al, 2010) — are around 10-times more likely to form on chronic than acute wounds: 60% and 6% respectively in one study (James et al, 2008). Biofilms are often relatively resilient to systemic antibiotics (Werthén et al, 2010), underscoring the importance of topical wound care.

Secondly, skin wounds typically harbour a diverse population of bacteria. In one study (James et al, 2008), *Staphylococcus* was the bacterial genus most frequently isolated from wounds, recovered from 65% of chronic wounds and 60% of acute wounds. Nevertheless, 13 different bacterial genera infected chronic wounds, compared with six genera isolated from acute wounds (James et al, 2008). Another study (Dowd et al, 2008), using sophisticated molecular analytical techniques, isolated numerous genera, including *Staphylococcus, Pseudomonas, Peptoniphilus, Enterobacter, Stenotrophomonas, Finegoldia* and *Serratia* species from biofilms in chronic wounds. Each wound type differed in the characteristic bacterial population. For example, 62% of bacterial types isolated from pressure ulcers were anaerobes, compared with almost 30% from diabetic foot ulcers. Molecular analysis also identified bacteria that are not usually recognised as wound pathogens, including *Abiotrophia para-adiacens* and *Rhodopseudomonas* species (Dowd et al, 2008). Therefore, a broad spectrum of action is a prerequisite for antibacterial wound care products and decolonisation.

Based on the evidence summarised in this paper, octenidine meets the need for a broad-spectrum antimicrobial suitable for wound care. For example, octenidine is more active than 4% chlorhexidine against *S aureus, Staphylococcus epidermidis, Proteus*

mirabilis, Streptococcus pyogenes, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Serratia marcescens and *Candida albicans* (Sedlock and Bailey, 1985). At concentrations of <1.5µM, octenidine reduced numbers of these bacteria by 99% within 15 minutes (Sedlock and Bailey, 1985). Schülke claim that octenilin wound irrigation solution is more effective than Prontosan® (B Braun) and Ringer's solution against biofilms (Schülke internal study report), although this study is not yet published. Importantly, low-level exposure for up to three months, a typical pattern of use in wound care, does not select MRSA strains that show stable octenidine resistance (Al-Doori et al, 2007).

However, the wound environment may modify bacteriological potency recorded in culture: 8% serum reduces the effectiveness of chlorhexidine between 2.5 and 35-fold (Siebert, 2010). *In vitro*, the addition of pus or 25% blood reduces chlorhexidine's effectiveness by around 1-log step. In contrast, blood (up to 10%), albumin and mucin do not undermine octenidine's efficacy (Siebert, 2010). This observation suggests that products containing octenidine retain antibacterial efficacy when applied to wounds.

Clinical efficacy and product characteristics

octenilin® wound irrigation solution

Octenilin wound irrigation solution is an isotonic formulation that removes debris, including microorganisms, necrotic tissue and dressing residues, and can facilitate dressing changes. The solution has a lower surface tension than Prontosan (betaine surfactant and polyhexanide) and Ringer's solution, which increases octenidine's contact time with the wound, and allows the formulation to reach fissures and pockets (Schülke internal study report).

Two studies exemplify the antibacterial effectiveness of octenidine solution in the wound care setting. Firstly, applying gauze dressings moistened with octenidine solution three times daily for three weeks to ulcers in 21 patients suffering from advanced cancer eradicated *S. aureus, S. epidermidis* and *P. mirabilis* from all wounds. *Enterococcus faecalis* persisted in two patients. *E. coli* and *P. aeruginosa* each persisted in one patient. However, no ulcer became infected and octenidine solution reduced necrosis, exudate, erythema and oedema (Sopata et al, 2008).

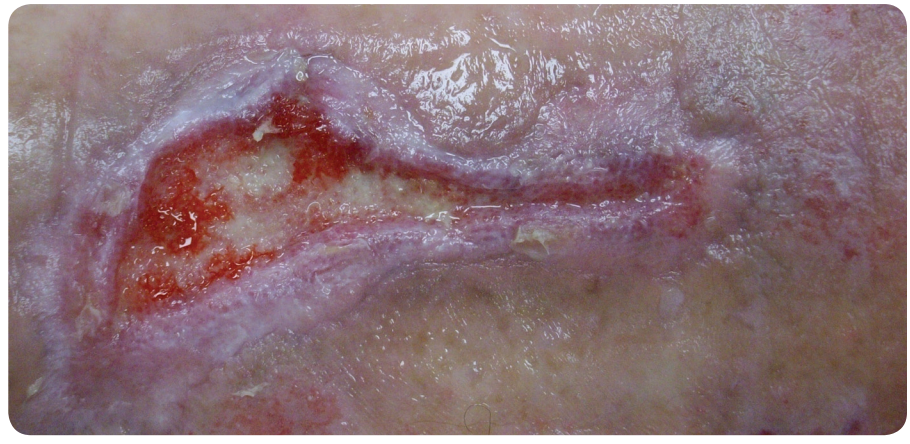

Figure 1. Wound before treatment with octenilin wound gel.

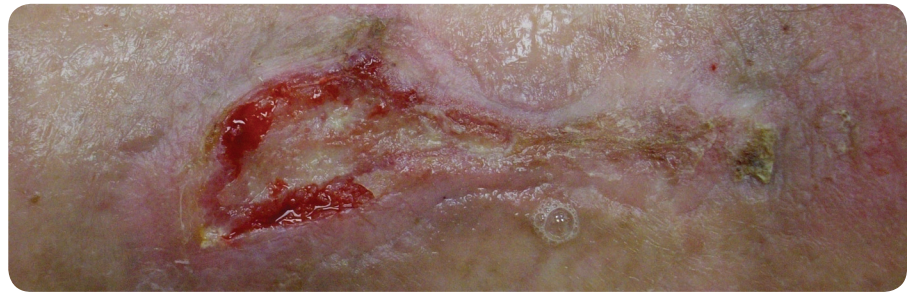

Figure 2. Wound after 12 days treatment with octenilin wound gel.

In the second study (Tietz, 2005), researchers measured bacterial density at 135 central venous catheter insertion sites in 62 severely immunocompromised patients following bone marrow transplantation. The bacterial density declined over time when octenidine solution was used during the dressing change. Most cultures became negative after two weeks. Six of these severely immunocompromised patients developed catheter-related bacteraemia, equivalent to 2.4 infections per 1000 catheter-days (Tietz, 2005).

Wound hydrogels

Wound hydrogels are cross-linked polymers, usually consisting of carboxymethylcellulose or starch monomers. The high water content (up to 96%) allows hydrogels to hydrate dry wound surfaces, which facilitates autolysis of necrotic or sloughy tissue. Hydrogels also absorb exudate, which helps prevent maceration (Jones and Milton, 2000; Trudgian 2000). Moreover, in contrast to irrigation fluids, hydrogels oxygenate the wound bed, which encourages release of growth factors that aid healing. Hydrogels also deliver nutrients more effectively than solutions (Trudgian, 2000).

In addition to the benefits common to hydrogels, octenilin wound gel's antibacterial activity further encourages healing of granulating and epithelialising wounds. Octenilin wound gel, a single use device that does not lose potency or facilitate microbial cross-contamination (Wright 2009), loosens even heavily encrusted coatings and releases 90% of the octenidine into the wound over 24 hours. Octenidine's preservative and bacteriostatic effects protect against wound pathogens and prevent further contamination for up to five days. This persistent effect may reduce redressing frequency (Schülke internal study report), although wound care teams could consider auditing this claim.

Indeed, preliminary results assessing octenilin wound irrigation solution and

wound gel in everyday practice are promising (Wright, 2009). A survey in 10 UK care homes collected 25 nurses' experiences of using octenilin wound irrigation solution and gel more than 200 times on at least 50 different residents. The products were most commonly used to treat pressure and vascular ulcers. All of the nurses agreed or strongly agreed that they were 'very content' with the performance of octenilin wound irrigation solution. All of the nurses also agreed or strongly agreed that the solution was well tolerated by residents and was effective at cleaning wounds. Over 70% agreed or strongly agreed that octenilin wound irrigation solution reduced the need for antibiotics. Similarly, over 90% agreed or strongly agreed that octenilin wound gel was effective at promoting wound healing. All nurses agreed or strongly agreed that octenilin wound gel was easy to use, well tolerated and that they were content with the product's performance (Wright, 2009). However, these results are subject to the biases inherent in surveys and the findings require confirmation in prospective studies and audits. Nevertheless, if confirmed, the reduction in need for antibiotics could help stem the rise in resistance.

octenisan® wash lotion

Around 20% of people with wounds show persistent *S. aureus* colonisation, while 60% are intermittently colonised. In many cases, colonisation precedes clinical bacteraemia (Popovich and Hota, 2008). In one study of patients presenting with *S. aureus* bacteraemia, 82% had blood isolates identical to those from their anterior nares (von Eiff et al, 2001). In a second study, 1% of patients with nasal *S. aureus* colonisation subsequently developed bacteraemia. In 86% of cases, the *S aureus* isolates — which microbiologists obtained when the patients presented with bacteraemia between one day and 14 months after taking the nasal sample — were clonally identical to those from the nose (von Eiff et al, 2001).

Due to the risk that colonised in-patients could import pathogens from the community, decolonisation can help prevent hospital-acquired infections. Octenisan is an antimicrobial hair and body wash that is available on general sale. Octenidine (0.2–1.6%) washes reduce levels of resident skin bacteria by 90.00% to 99.98%, depending on the concentration and number of applications (Sedlock and Bailey, 1985). In an unpublished 14-day study, Octenisan wash lotion persistently eradicated MRSA in 78% of 45 patients (Schülke internal study report). Infection control teams could consider asking local pharmacists to suggest that patients attempt decolonisation before admission to hospital.

Cytotoxicity

Cytotoxicity offers a surrogate for tolerability in the wound. However, differences in experimental protocols complicate both the comparison of products and deciding whether the results are clinically significant. For example, Kramer et al (2004) compared a product containing polyhexanide, an octenidine-based formulation (octenisept®, [Schülke] not available in the UK) and Ringer's solution in experimental superficial aseptic skin wounds in piglets. The paper describes Ringer solution, the vehicle for the polyhexanide formulation, as a placebo. However, the study did not assess untreated control wounds or the vehicle for octenisept, which may compromise the study's relevance to the UK. Furthermore, the concentrations of octenidine (1% octenidine) are higher in octenisept than in octenilin wound gel (0.05% octenidine) and octenilin wound irrigation solution (0.05% octenidine). These caveats notwithstanding, no significant histological differences emerged at any time between the three groups (Kramer et al, 2004), supporting suggestions that the regimens show benign cytotoxicological profiles.

However, cytotoxicity studies often produce inconsistent results, which can complicate attempts to translate the results into the clinical setting. For example, Ince et al (2007) exposed human fetal osteoblast cells (hFOB 1.19) and human endothelial cells (EAhy 926) to gentamicin (12.5–800µg/ml) and polyhexanide (0.0006–0.01%) *in vitro*. Despite the dose of polyhexanide being of 'questionable antibacterial activity', the cells showed severe damage, reduced viability and declined in number. In contrast, gentamicin did not induce cytotoxicity. Moreover, three further studies suggest that octenisept has a low propensity for cytotoxicity and does not impede wound healing.

Firstly, Müller and Kramer (2008) reported that octenidine shows a more favourable balance of antibacterial activity against *E. coli* and *S. aureus* to cytotoxicity on cultured fibroblasts than benzalkonium chloride, cetylpyridinium chloride, chlorhexidine digluconate, mild silver protein, polyhexamethylene biguanide, povidone iodine solution and ointment, silver nitrate, silver sulfadiazine and triclosan.

Secondly, an *in vivo* study in pigs (Stahl et al, 2010) showed that octenisept did not retard wound healing or compromise healing rate under occlusive or non-occlusive conditions, compared with povidone-iodine, vehicle treatment as well as untreated controls. Wound inflammation resolved more rapidly without occlusion (Stahl et al, 2010).

Finally, Vanscheidt et al (2005) treated chronic ulcers in 43 patients with octenisept or Ringer's solution for four weeks. Octenisept reduced signs of infection and significantly improved granulation without adversely affecting wound healing compared to Ringer's solution.

Differences in experimental protocols probably contribute to the inconsistencies between the studies. Furthermore, Kramer et al (2004) assessed octenisept. As mentioned above, this formulation is not available in the UK and contains phenoxyethanol, which, in some models, (e.g. human neuroblastoma SH-SY5Y) concentration-dependently compromises cell viability and either initiates or exacerbates cytotoxicity (Regulska et al, 2010). In contrast, octenilin and octenisan do not contain phenoxyethanol or any other alcohol. Therefore, the relative contribution of octenidine and phenoxyethanol to impaired wound

contraction or cytotoxicity in the studies assessing octenisept is unclear, as is the clinical relevance to alcohol-free formulations, such as those available in the UK. Similarly, the polyhexanide-containing formulation assessed by Kramer et al (2004) is not commercially available in the UK.

The reasons for the differences between the studies, the relevance of cytotoxicological findings in experimental models to clinical practice, and whether the differences revealed by these models are clinically significant in the clinical chronic wound setting remains unclear. Such discrepancies underscore the importance of auditing outcomes in clinical practice. In the meantime, it seems premature to conclude that, for example, polyhexanide and octenidine differ significantly in cytotoxic potential, or produce differential effects on wound healing in the clinic. Clearly, further studies are needed.

Conclusion

Octenidine is a unique, innovative antimicrobial with a broad spectrum of action that encompasses multi-drug resistant strains. Experimental evidence, clinical trials and experience (Schülke launched octenisan in 2005 followed by octenilin wound gel and irrigation solution in 2008) reviewed in this paper show that octenidine is effective, well tolerated and does not, in most studies, show a propensity to cause cytotoxicity or hinder wound healing. Further studies are needed to determine whether commonly used wound care products differ in cytotoxic potential, as well as the clinical significance of *in vitro* and experimental wound healing models. Overall, octenilin wound irrigation solution and wound gel and octenisan wash lotion offer valuable options to reducing the burden arising from hospital-acquired infections and enhance wound healing. **WUK**

Key points

- Octenidine, a broad-spectrum antimicrobial that encompasses multi-drug resistant strains, is currently available as a gel, irrigation solution and body wash for decolonisation.
- Prolonged, low-level exposure does not select MRSA strains, exhibiting stable octenidine resistance.
- Octenilin wound irrigation solution and wound gel are effective and well tolerated antibacterial agents that can be used in a range of settings including burns, pressure and leg ulcers. Decolonisation with octenisan wash lotion could reduce pathogen carriage from the community into hospital.
- Octenidine shows a more favourable balance of antibacterial activity to cytotoxicity, and, in most studies, shows a low propensity to hinder wound healing.

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