A new silver dressing for wounds with delayed healing

Bacterial colonisation and infection are considered to contribute to delayed healing. Silver-medicated dressings are recommended for the management of critically colonised wounds. This paper describes the properties and clinical use of a new low-adherent dressing manufactured from a metallic silver-coated polyamide fabric. It exerts antibacterial activity over nine days with minimal keratinocyte toxicity. Data from an observational, descriptive outpatient study demonstrate its efficacy for stimulation of healing in a wide range of previously non-healing wounds.

Keith Moore

KEY WORDS
Atrauman Ag
Chronic wound
Critical colonisation
Wound infection
Silver dressing

Intact normal skin is colonised with bacterial flora. It would seem almost inevitable that if dermal healing is delayed then the extended exposure to bacteria on adjacent skin and in the environment will lead to colonisation of the wound. This may not necessarily impede healing. Low levels of bacteria may have no effect on wound closure. However, problems arise when the numbers of pathogenic bacteria in the wound increase in number.

A Wound Infection Continuum (Kingsley, 2003) is considered to exist where the presence of increasing numbers of bacteria can lead to four states:

- Contamination
- Colonisation
- Critical colonisation
- Infection.

Acute and chronic wounds are likely to be contaminated or colonised by a wide variety of aerobic and anaerobic organisms. Their proliferation is dependent upon both the ability of their immediate environment to provide suitable nutritive and physical support for growth and their ability to evade the host immune response. Bacterial survival and proliferation is therefore a balance between the virulence of an organism and host resistance (Bowler et al, 2001). Chronic wounds may rapidly shift towards critical colonisation as a consequence of changes in the host immune response or ingress of additional bacterial species (Cooper and Lawrence, 1996). Where it is not possible to maintain a balanced situation because of immune compromisation or co-morbidity then colonisation may progress towards critical colonisation and infection resulting in delayed healing (Schultz et al, 2003).

Realisation of the important role that bacteria play in delayed healing, combined with the difficulties of a clear definition of when to intervene...is likely to lead to the increasing prophylactic use of antimicrobial treatment strategies.

It is suggested that critically colonised and infected wounds should be treated with topical antimicrobials, and infected wounds with additional antibiotic therapy (Kingsley, 2001). Treatment of critically colonised chronic wounds with antibacterial dressings has been demonstrated to produce clinical improvement and accelerated healing (Sibbald, 2001) with a decrease in surface bacterial numbers.

An overtly infected wound can be identified by observed clinical symptoms (Cutting and Harding, 1994) but by definition, a critically colonised wound will not exhibit the classical signs of infection. One of the challenges faced by practitioners is defining where a wound lies on the infection continuum (Kingsley, 2001) in order to identify when therapeutic intervention is required to pre-empt the effect of increased bacterial burden on healing.

Bacteriology alone does not assist in defining when to treat with anti-microbials and a holistic assessment of the patient is required to define wound infectious status (Cooper, 2005). Regardless of the difficulties of identifying where a wound lies on the infection continuum, decreasing the bacterial load of wound tissue is seen as one of the cornerstones of the preparation of the wound for healing (Schultz et al, 2003).

Keith Moore is a Freelance Scientist, WoundSci, PO Box 32, Usk, Monmouthshire, NP15 1YU

Realisation of the important role that bacteria play in delayed healing combined with the difficulties of a clear definition of when to intervene, especially with regard to critical colonisation, is likely to lead to increasing prophylactic use of anti-microbial treatment strategies. The rising incidence of resistance to antibiotics mitigates against their wider use for critically colonised wounds and practitioners have to seek alternatives where resistance is less of an issue. Such alternatives include antimicrobial agents, especially those that can be incorporated into dressings for release into the wound environment.

Silver as an antibacterial agent is particularly attractive because it can readily be incorporated into dressing materials. It is suggested that silver should be utilised when critical colonisation occurs (White, 2001). Despite the increasing use of silver in wound management, there is little evidence of emerging resistance (Percival et al, 2005). These authors make the interesting point that bacteria have been exposed to low levels of silver in the natural environment for over 4 billion years without significant resistance evolving whereas widespread antibiotic resistance has developed within 60 years of their introduction.

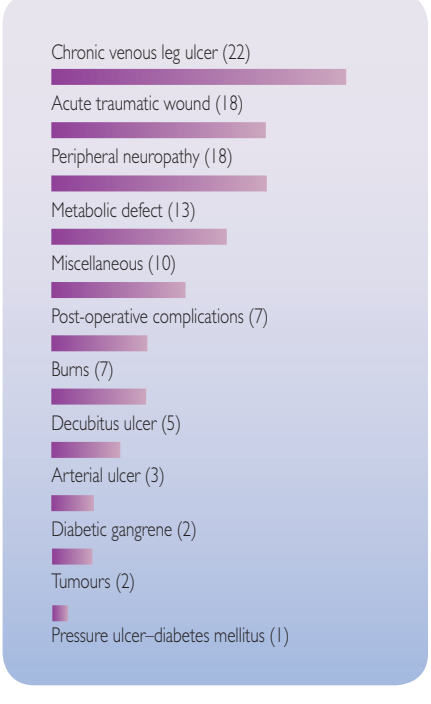

Figure 1. Wound aetiology. Number of wounds in parentheses; total wounds = 87 (one patient had two wounds); Multiple entries were possible.

The performance characteristics of a new dressing, Atrauman Ag (Paul Hartmann Ltd, UK) and its use for treatment of longstanding wounds of diverse aetiology are described in this paper. Atrauman Ag sustains delivery of a level of silver for nine days that maintains anti-bacterial activity with minimal wound cell toxicity. The clinical data generated by a preliminary observational study demonstrate its ability to promote healing and reduce wound pain during three dressing applications.

Bacteria have been exposed to low levels of silver in the natural environment for over 4 billion years without significant resistance evolving, whereas widespread antibiotic resistance has developed within 60 years of their introduction.

Dressing properties

Atrauman Ag is a low-adherent tulle dressing manufactured from a metallic silver-coated polyamide fabric impregnated with neutral lipids. The dressing is non-medicated, contains no paraffin and leaves no residue. It is recommended for the management of burns, traumatic wounds, skin donor sites and chronic wounds such as lower leg ulceration and for prophylaxis against potential infection.

Antibacterial activity

Atrauman Ag has been demonstrated in vitro to be effective in killing a range of pathogenic bacteria and those commensal organisms normally found on the skin (Ziegler et al, 2006). *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *S. epidermidis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Bacillus subtilis* were all reduced in number by at least 10 000-fold during a 24-hour period of contact with Atrauman Ag in a standard bacterial kill assay. Taking the standard assay one step further, Ziegler et al (2006) demonstrated that the dressing maintained its antibacterial properties over a nine-day period even when the same dressing sample was challenged on a daily basis with fresh viable bacteria. This test was conducted with *S. aureus* and a 100% reduction of bacteria was found for each 24-hour period.

Biocompatibility

For silver dressings to exert their antibacterial effect, the silver in the dressing has to be released into the wound environment as biologically active ions (Lansdown, 2004). As well as killing bacteria by disrupting normal cell function, such as respiration and inactivating bacterial DNA and RNA, it can also be toxic for cells such as fibroblasts that are involved in healing (McCauley et al, 1989). This means the dressing needs to achieve an optimum concentration of silver in the wound which exerts an antibacterial effect without imposing a toxic effect that may impede healing.

This can be addressed by regulating the release of silver from the dressing through controlling the amount of silver present, its particle size and chemical formulation. Ziegler et al (2006) found that Atrauman Ag achieves an appropriate balance by demonstrating that, in addition to the antibacterial activity described above, it was minimally cytotoxic for cultured keratinocytes compared with two other silver dressings, one of which reduced keratinocyte viability by 98%.

Clinical efficacy

Methods

An observational, descriptive outpatient study was performed to assess the clinical effectiveness of Atrauman Ag for the treatment of a variety of non-healing wounds of varying aetiology as shown in *Figure 1*. The study was performed following the guidelines of the Ethics Committee of the Landesärztekammer Baden-Württemberg, Germany (Baden

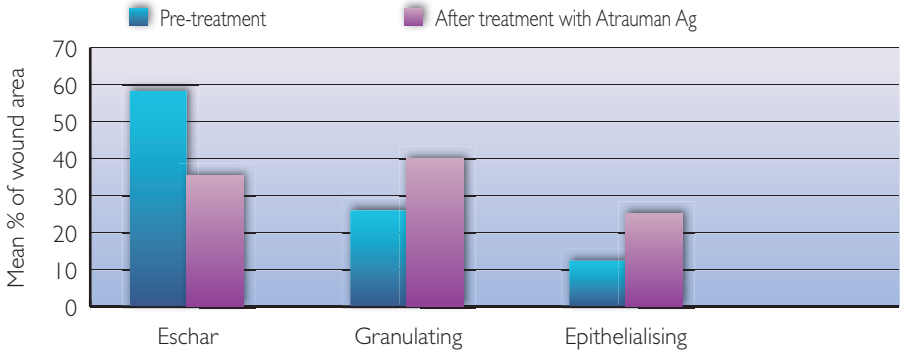

Figure 2. Effect of treatment with Atrauman Ag on wound appearance.

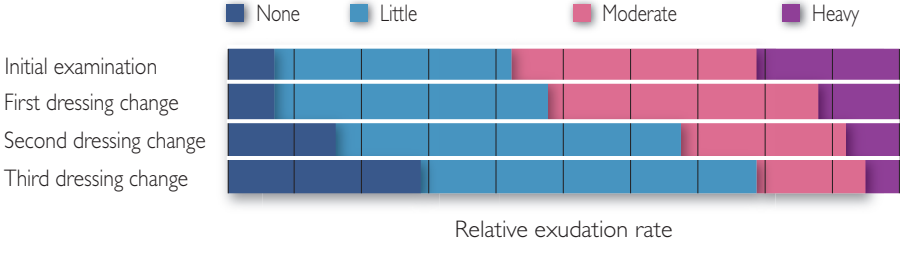

Figure 3. Effect of Atrauman Ag on wound exudation.

Wurttemberg Medical Association). Patients and their wounds were assessed using a questionnaire to capture the following information: age; sex; general health; wound type, condition, duration and location; previous treatment; and concomitant medication. At initiation and completion of treatment the amount of wound eschar and degree of granulation and epithelialisation were assessed. Exudation, wound margin condition, wound pain and clinical signs of infection were assessed at each dressing change.

At the conclusion of treatment with Atrauman Ag, clinicians were asked to describe the performance of the dressing and whether it had fulfilled their clinical expectations. Patients were asked to give an evaluation of dressing tolerance, comfort and overall impression, including whether the dressing met their expectations for treatment.

Patients

Eighty-six patients were recruited from 16 centres. The average age was 73 years; 64% were female and 25% were considered to have poor general health.

Wounds

Two-thirds of the patients suffered from chronic wounds and the dressing was used most frequently to treat leg ulcers (31%). Chronic venous leg ulcers were the largest single group tested and other aetiologies included acute traumatic wounds and wounds caused by peripheral neuropathy and delayed healing as a consequence of metabolic defects (*Figure 1*). On average the wounds had existed for one year and the mean size was 4cm x 3.3cm.

Before their inclusion in the study the wounds had been treated with a variety of dressings. In 29 cases, no dressing had previously been applied. About half of the patients (47%) were being treated with compression therapy and 17% with a pressure-relieving device. Topical ointments were being used to treat 13 of the ulcers and secondary dressings included gauze and foams. Sixty percent of the study participants were receiving concomitant medication including anticoagulants (13%), NSAIDS (12%), systemic steroids (1%), immunosupressants (1%) and 49% miscellaneous (predominantly, anti-hypertensives, diuretics, analgesics and anti-diabetics).

Treatment

Atrauman Ag was selected for use for a variety of reasons including: previous treatments being unsuccessful (39.1%), treatment of a chronic (26.4%) or recurrent (13.8%) wound and intolerance of previous treatments. The patients were treated for between three and 21 days (mean = 8 days) with three changes of dressing. The time between dressing change was, on average, three days with a maximum wear time of 15 days.

Wound assessments

Before initiating treatment with Atrauman Ag, an average of 59.2% of the wound surface was coated with eschar, 27% of the wound area was granulating and 12.1% of the wound was re-epithelialising. Improvements in all three parameters were observed after three treatments (*Figure 2*) so that the final assessment showed a decrease in eschar to 35.8% and an increase in granulation tissue and epithelialising areas to 40% and 25%, respectively. As a consequence of the increased re-epithelialisation, average wound size decreased so that the initial average size of 4cm x 3.3cm was reduced to 0.7cm x 0.6cm after three applications of Atrauman Ag.

Judged by clinical criteria, 24% of the 87 wounds treated with Atrauman Ag were initially infected. This number decreased to 14% by the first dressing

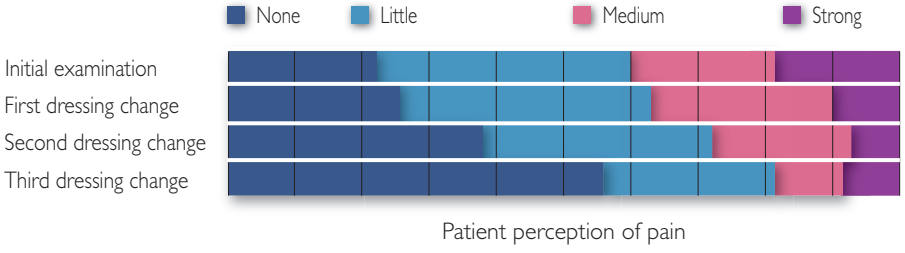

Figure 4. Effect of Atrauman Ag on wound pain.

change, 11% by the second and 8% after the three dressing changes. This reduction in rate of infection was accompanied by a decrease in overall exudation (*Figure 3*). Initially only 7% of the wounds were non-exuding. By the end of treatment, this had risen to 28.7%. This was matched by a decrease in heavily exuding wounds from 19.5% to 2.3%.

In addition to the changes observed in the wound bed, improvements were also noted in the peri-wound margins. Before treatment with Atrauman Ag, 23% of the wounds had oedematous wound margins with 39.1% exhibiting erythema. After the three dressing changes these figures had decreased to 12.6% and 25.3%, respectively. This coincided with reductions in the number of patients with reduced maceration (13.8% to 4.6%) and eczema (10.3% to 3.4%).

Pain assessment

Treatment with Atrauman Ag progressively reduced wound pain. Before treatment, 28.1% of patients said they were pain-free, whereas after three dressing changes, 47.1% reported no wound pain. Pain intensity also decreased (*Figure 4*) as well as the total number of patients with pain. Initially 21.8% reported moderate pain and 16.1% strong pain. For those patients who still reported pain at the end of the study, these figures were reduced to 10.3% and 5.7%, respectively.

Product assessment

Performance of the dressing was reviewed by clinicians and patients participating in the study. After the final wound assessment, examining clinicians stated that the condition of 83% of the wounds had improved compared with the first assessment. The clinicians' expectations of the wound dressing were either exceeded or fulfilled in 75% of cases. Only 15% of the clinicians were of the opinion that Atrauman Ag had not influenced wound status positively and 7% felt that they expected more from the dressing. The average assessment of dressing use was 91.7% good or very good with 94% of clinicians also saying that ease of dressing removal was good or very good with no adherence to the wound bed. The clinicians' overall impression of Atrauman Ag was judged to be very good by 36.9%, good by 48.8% and 14.3% assessed it as satisfactory.

Patients also gave a positive response to dressing use. Tolerance and comfort during wear was assessed by 90% as very good or good. The patients' overall impression of Atrauman Ag was assessed as very good by 45.8% of subjects and good by 39.8%. The dressing fulfilled or exceeded the expectations of more than 70% of the patients with less than 10% stating that their expectations were not quite fulfilled and 3.7% saying they were not fulfilled at all.

Conclusion

As discussed earlier, the use of a dressing that delivers silver as a topical anti-microbial has a number of advantages (Lansdown, 2004):

- Silver can kill a broad range of aerobic and anaerobic bacteria
- It can be incorporated in dressings to ensure continuing delivery to the wound
- Resistance occurs infrequently
- In low concentrations silver is non-toxic to host cells
- It may exert anti-inflammatory effects.

Key Points

- The treatment of critically colonised chronic wounds with antibacterial dressings has been demonstrated to produce clinical improvement and accelerated healing.
- Silver should be utilised when critical colonisation occurs because of the problems associated with antibiotic resistance.
- There is little evidence of emerging bacterial resistance to silver.
- Atrauman Ag sustains antibacterial activity for nine days.
- The level of silver released by Atrauman Ag is bactericidal with minimal toxicity for wound cells.
- Treatment of hard-to-heal wounds with Atrauman Ag for up to 21 days (with three dressing changes), decreased infection and exudation and increased granulation and re-epithelialisation with a resulting marked reduction in wound size.
- The number of painful wounds and pain intensity decreased during treatment with Atrauman Ag..

Case study

Atrauman Ag can be used as a prophylaxis against infection or as a supplementary intervention in combination with systemic antibiotic therapy. This case study is presented to demonstrate how its continuing antibacterial action can promote healing.

An 80-year-old male underwent excision of his fourth toe due to osteomyelitis and post-operatively developed a wound infection. He complained of occasional wound pain and before the application of Atrauman Ag was receiving treatment with amoxicillin. Ten days after surgery the wound measured 3.5 x 2cm, some eschar was present and the granulation tissue was in poor condition (Figure 5). Atrauman Ag was applied with PermaFoam (Paul Hartmann AG, Germany) as a secondary dressing that was initially changed daily. After four days treatment with Atrauman Ag the attending clinician considered that the infection had subsided and stopped the course of antibiotics.

The condition of the wound continued to improve with treatment. As the eschar reduced, the wound began to granulate and the wound area decreased as re-epithelialisation commenced. After % epithelialised (*Figure 6*) and after 7 weeks of treatment with Atrauman Ag the wound healed (*Figure 7*).

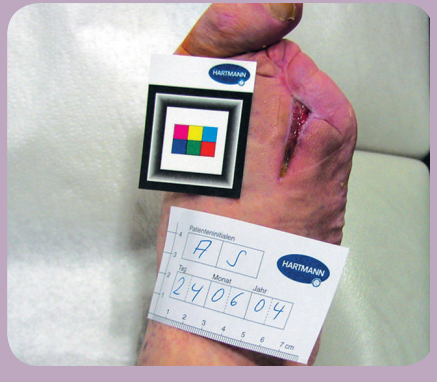

Figure 5. Before treatment with Atrauman Ag. At initial examination the wound measured 3.2 x 2cm, the wound bed was 20% eschar, 40% granulation tissue and 40% epithelial tissue.

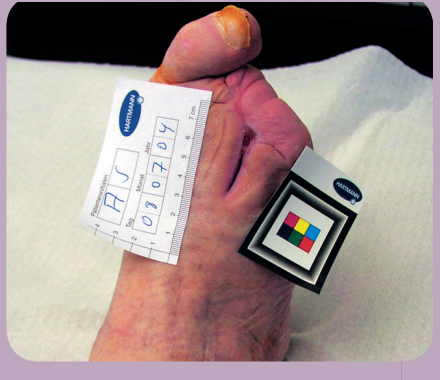

Figure 6. Wound improvement after two weeks treatment. Eschar is no longer present and the wound is 50% granulation tissue, 50% epithelial tissue.

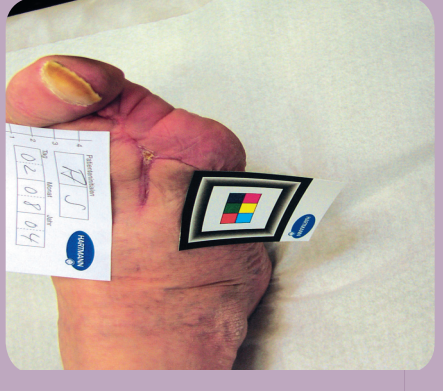

Figure 7. The wound healed after 7 weeks of treatment.

One potential problem associated with the use of silver may be its toxicity for cells involved in the healing process. In vitro testing has shown that silver sulphadiazine can inhibit fibroblast proliferation (McCauley et al, 1989) and at least one silver containing dressing is toxic for keratinocytes (Ziegler et al, 2006). While the risks of systemic lasting tissue damage consequential to silver anti-microbial therapy are low (Lansdown and Williams, 2004), it may be that at the wound microenvironment level a balance has to be sought between achieving a sufficient concentration of silver ions that will kill bacteria but that will not be toxic.

For Atrauman Ag, the manufacturer has produced a dressing formulation that will deliver sufficient silver ions over a nine day period to kill a broad spectrum of bacteria with minimum toxicity for cells that are important in driving the wound towards healing. These in vitro data are translated into clinical reality by the clinical observations found during treatment of a group of 87 non-selected wounds of varying aetiology that had previously proven hard-to-heal with an average duration of one year. A course of treatment with three changes of Atrauman Ag over a period of 3–21 days resulted in a marked improvement in parameters associated with delayed healing, such as the presence of infection and eschar. The proportion of granulating tissue was increased and re-epithelialisation stimulated to produce a reduction in wound size from a mean of 4cm x 3.3cm to 0.7cm x 0.6cm during the study period. At the same time, peri-wound areas improved with reduction in erythema, oedema and maceration.

Expectations of dressing performance were fulfilled by the overwhelming majority of clinicians and patients involved in the study. Eighty five percent of the clinicians felt that Atrauman Ag had positively influenced the wound and over 90% stated that ease of removal and

overall performance was good or very good. Patients also gave a positive response to dressing use with 85% assessing its performance as good or very good. Of particular significance for the patient was the progressive reduction in painful wounds and intensity of pain with successive applications of the dressing.

In vitro testing has shown that the new silver releasing dressing, Atrauman Ag, has a superior profile of anti-bacterial activity over toxicity (Ziegler et al, 2006). The data from a preliminary observational study presented here demonstrate its efficacy in treating a diverse range of hard-to-heal wounds thus indicating its value for prophylactic anti-bacterial therapy. WUK

References

Bowler PG, Duerden BI, Armstrong DG (2001) Wound microbiology and associated approaches to wound management. *Clin Microbiol Rev* **14(2):** 244–69

Cooper R, Lawrence JC (1996) The role of antimicrobial agents in wound care. *J Wound Care* **5(8):** 374–80

Cooper RA (2005) Understanding wound infection. In: European Wound Management Association (EWMA). Position Document: Identifying criteria for wound infection. MEP, London: 2–5

Cutting KF, Harding KG (1994) Criteria for identifying wound infection. *J Wound Care* **3(4):** 198–201

Gupta A, Matsui K, Lo JF, Silver S (1999) Molecular basis for resistance to silver cations in Salmonella. *Nat Med* **5(2):** 183–8

Kingsley A (2001) A proactive approach to wound infection. *Nurs Stand* **15(30):** 50–4, 56, 58

Kingsley A (2003) The wound infection continuum and its application to clinical practice. *Ostomy Wound Manage* **49(7A Suppl):** 1–7

Lansdown AB (2004) A review of the use of silver in wound care: facts and fallacies. *Br J Nurs* **13(6 Suppl):** S6–19

Madden MR, Nolan E, Finkelstein JL, Yurt RW, Smeland J, Goodwin CW, Hefton J, Staiano-Coico L (1989) Comparison of an occlusive and a semi-occlusive dressing and the effect of the wound exudate upon keratinocyte proliferation. *J Trauma* **29(7):** 924–30

McCauley RL, Linares HA, Pelligrini V, Herndon DN, Robson MC, Heggers JP (1989) In vitro toxicity of topical antimicrobial agents to human fibroblasts. *J Surg Res* **46(3):** 267–74

Percival SL, Bowler PG, Russell D (2005) Bacterial resistance to silver in wound care. *J Hosp Infect* **60(1):** 1–7

Schultz GS, Sibbald RG, Falanga V, et al (2003) Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* **11 (Suppl 1):** S1–S28

Sibbald RG, Browne AC, Coutts P, Queen D (2001) Screening evaluation of an ionized nanocrystalline silver dressing in chronic wound care. *Ostomy Wound Manage* **47(10):** 38–43

White RJ (2001) An historical overview of the use of silver in wound management. *Br J Nurs* **(Silver Suppl 1):** 3–9

Ziegler K, Gorl R, Effing J et al (2006) Reduced cellular toxicity of a new silver-containing antimicrobial dressing and clinical performance in non-healing wounds. *Skin Pharmacol Physiol* **19(3):** 140–6