



## The use of cerium nitrate-silver sulphadiazine as a topical burns dressing

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**SUMMARY.** Infection remains the major cause of morbidity and mortality following the shock phase in the burn patient. Measures to reduce the risk of wound infection and subsequent sepsis include early excision where possible, and the use of topical antimicrobial creams such as silver sulphadiazine. Studies from the USA and Europe suggest the addition of cerium nitrate to this commonly used agent may improve its efficacy.

We present the findings of a pilot study which investigated the action of a commercial preparation of cerium nitrate/silver sulphadiazine mixture (Flammacerium, Duphar B.V. Holland) on 20 patients considered unsuitable for surgery. There were no episodes of cellulitis or septicaemia. Flammacerium was noted to produce an adherent eschar that was easy to shave and which received split skin grafts well.

Following the shock phase, sepsis remains the major cause of morbidity and mortality in the burned patient. Whilst the benefits of early surgery for burn wounds are agreed, early or total excision of the injured area(s) may not be feasible due to the patient's fitness for surgery or the extent of his or her burns. Other prophylactic measures include the use of antibacterial creams. Flamazine (1% silver sulphadiazine, Smith & Nephew Ltd) is the most widely used topical agent in the UK, providing broad spectrum activity against *pseudomonas aeruginosa* and other gram negative organisms. However, despite its use, patients still succumb to the complications of local and disseminated infection. Furthermore, prolonged use of this cream has been noted to produce an uneven, macerated eschar which is difficult to shave and in which bacterial proliferation may occur (Fig. 1).

Evidence from both animal and human studies has suggested that cerium nitrate confers an added antibacterial action when used topically, either alone or as part of a cream complex with silver sulphadiazine. The latter combination, Flammacerium (Duphar B.V.

Holland), is used extensively in the Netherlands and other European countries.

We have been provided with the first supplies of Flammacerium for preliminary assessment in a British burns unit. This paper presents the findings of a pilot study performed to clarify the role of cerium nitrate-silver sulphadiazine as a topical agent.

### Patients and methods

Over a 16-week period, 98 patients were admitted to the burns unit at Queen Mary's University Hospital. Of those presenting with deep dermal or full thickness burns, 20 were considered unsuitable for early or complete excision on the basis of: (a) their medical status, or (b) the extent of their burns.

The patients in this group presented with burns ranging from 1-30% in body surface area (mean 13.4%). Their ages spanned from 5 months to 87 years.

Patients were included in this study if they were over 2 years of age and seen within 12 h of injury. On admission a microbiology swab was taken of the wound, which was then irrigated with aqueous chlorhexidine. Flammacerium was applied directly to the wound on gauze and secured with either a crepe bandage or net dressing. The dressings were changed daily. On alternate days wound swabs were repeated prior to redressing and this was repeated for up to 28 days post-injury.

### Results

Four deaths occurred in this group; 3 were predicted and followed severe inhalation injuries. The fourth death occurred in a frail 87-year-old woman due to broncho-pneumonia 7 weeks post-burn (her burns had fully healed following grafting).



Fig. 1

**Figure 1**—Typical appearance of burn wound following prolonged use of silver sulphadiazine.



Fig. 2

Figure 2—Dry, adherent eschar produced by cerium nitrate-silver sulphadiazine (Flammacerium).

Three patients had burns which were treated conservatively and healed spontaneously. The remaining 14 patients were discharged home with healed burns following late excision and grafting.

There were no deaths from infection, nor were there any septicaemic episodes or cellulitis. No clinical evidence of sub-eschar sepsis was noted at the time of excision.

In all but one (95%) of the patients studied, the eschar was observed to be dry, adherent and free of granulation tissue throughout the period that Flammacerium was used (Fig. 2). Furthermore, once excised, the resultant bed was clean and allowed an excellent take of graft (approximately 90% when reviewed at 10 days postoperatively).

Figure 3A shows the cumulative prevalence of Gram positive organisms in cultures obtained from serial wound swabs. *Staphylococcus aureus* was isolated in the burn wounds of 15 patients (75%; 60% within 4 days). The continued use of Flammacerium did not affect this high yield, as patients remained colonised once infected, but this appeared to be of limited clinical significance. Eight patients grew *streptococcus faecalis*, acquisition occurring on average 72 h later

than *staphylococcus aureus*. Group B, non-haemolytic streptococci, were isolated in 2 patients.

Figure 3B shows the acquisition of Gram negative organisms using the same axes as in Figure 3A. Thirty per cent of patients grew *pseudomonas aeruginosa*, typically appearing at a later stage than the Gram positive staphylococci. *Acinetobacter* was isolated in 2 patients.

### Discussion

Silver sulphadiazine cream was introduced in 1968 and has gained widespread acceptance as a topical antibacterial for use on burn wounds. It has undoubtedly benefits as a prophylactic agent, but the recent impression in this unit has been that it performs less well once colonisation of the burn wound is established. Moreover, like many other cream dressings it produces a macerated eschar which is difficult to excise cleanly in preparation for grafting.

Heavy metal ions were first investigated for their antibacterial activity several decades ago.<sup>1</sup> The rare earth metal cerium occupies atomic number 58 on the periodic table and has several laboratory and industrial uses, but has no medical application other than that discussed in this paper.

Cerium nitrate was first described as a burn dressing component in 1976 by Monafó, who used it both alone and mixed with silver sulphadiazine cream.<sup>2</sup> This and later studies by Monafó confirmed the efficacy of the combined preparation; a series of patients was accumulated and discussed in several papers published between 1976 and 1983, with similar findings in an increasingly large population.<sup>3-5</sup> These findings may be summarised as a lower than expected prevalence of bacterial colonisation, fewer septic complications and an overall mortality almost 59% lower than predicted from Bull and Fisher's tables. Absorption of cerium was unmeasurable and the adverse effects of the mixed cream, such as methaemoglobinaemia and skin sensitivity, were sufficiently rare as to be regarded as of theoretical importance only.<sup>6</sup>

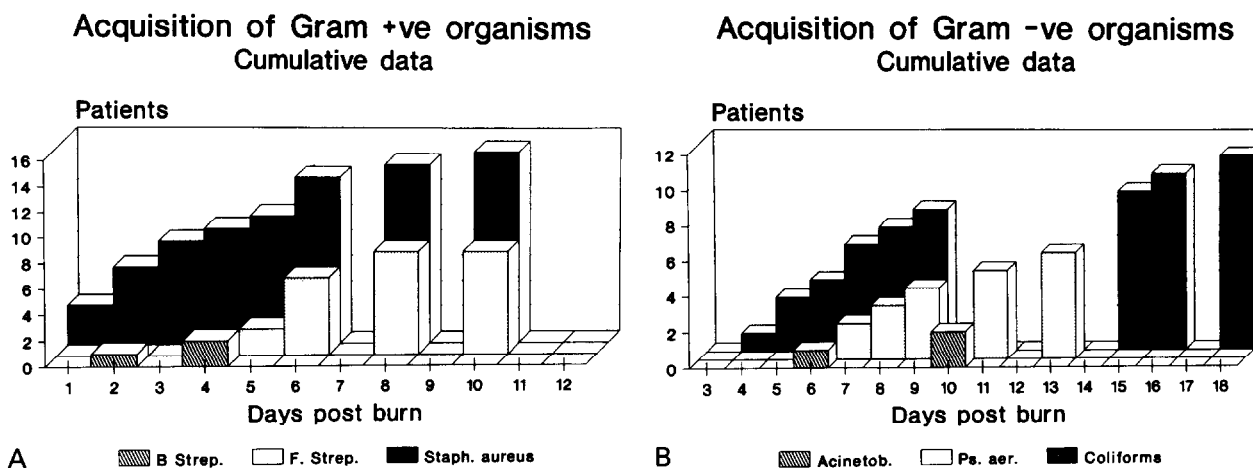


Fig. 3

Figure 3—Graphs to show the cumulative prevalence of Gram positive and negative organisms.

Over the same period other studies were published which questioned the role of cerium. A prospective trial carried out by Munster showed no difference in mortality or in bacterial proliferation between dressings consisting of a combined preparation of silver sulphadiazine and cerium nitrate, and silver sulphadiazine alone.<sup>7</sup> Other studies produced similar findings.<sup>8</sup>

Experience in Europe has been more positive with several authors commending the use of cerium nitrate; Hermans compared bacterial growths on bilateral burns treated with silver sulphadiazine on one side and added cerium nitrate on the other. He found significantly fewer heavy growths on the cerium side.<sup>9</sup> Boeckx found this combined cream to be superior to a chlorhexidine-medicated jelly in controlling *Pseudomonas* on burn wounds with, in addition, a lower incidence of clinically apparent infections in the cerium-treated patients.<sup>10</sup>

Wasserman *et al.* investigated a small group of patients with burns of over 50% body surface area who had been treated with combined silver sulphadiazine-cerium nitrate cream. They recorded the survival of a larger number of patients than might have been predicted from historical controls.<sup>11</sup>

The most striking clinical feature of adding cerium nitrate to silver sulphadiazine cream, seen in our and other studies, is the effect on the burn eschar. It is claimed the eschar acts as a stable barrier to bacterial invasion, over many weeks if necessary, following which it may be easily shaved. Although our sample population was small, the low incidence of wound infection was still noteworthy, as was the prolonged action of the combined cream over periods of up to 4 weeks; this would tend to confirm the 'protective' effects of the eschar.

These favourable results have been attributed to several factors; some cerium salts are antibacterial *in vitro*, although there is controversy as to the effect of combining them with silver sulphadiazine, and several hypothetical mechanisms to its route of action have been proposed.<sup>2,9</sup> Topical cerium nitrate has been shown to prevent post-burn suppression of cell-mediated immunity as measured by mouse ear swelling in response to 2,4-dinitrofluorobenzene challenge; it was suggested that the mechanism of this effect may be the result of the complexing of one or more cutaneous burn toxins by the cerium salt.<sup>12</sup> Recent work has shown combined silver sulphadiazine-cerium nitrate to produce a calcium-rich layer on the surface of dermal burns and this is thought to follow cerium-induced sequestration of pyrophosphate, facilitating precipitation of calcium salts.<sup>13</sup> The resultant 'shell'-like layer acts as a bacterial barrier and coupled with a dry wound minimises infection. This study also noted the low infiltration of polymorpholeucocytes (PMN) into burn wounds treated with this combined preparation, which may account for the dryness of the burn

eschar as opposed to the macerated wound associated with silver sulphadiazine, where PMN infiltration is prevalent.

The results of this pilot study confirm the experience of other groups and suggest that a combined preparation of cerium nitrate and silver sulphadiazine may confer marked benefit to the burns patient when a topical antimicrobial agent is indicated.

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