THE USE OF SILVER SULFADIAZINE IN THE TREATMENT OF BURNS—A REVIEW OF 179 CASES

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INTRODUCTION

Until recently, the overall mortality rate for burns has been 40% even in specialised treatment centres and in the more extensive cases, it has been prohibitively high (Gallone, 1969). Not until the last decade was it conclusively shown that invasive bacterial infection originating in the burn wound was the cause of death in three-quarters of the autopsies performed in burn centres (Teplitz, 1964). In burns of 50% or more of the body surface, infection can be overwhelming and most deaths in the past have been caused by septicaemia. Infection also increases the morbidity in burns by augmenting burn anemia and malnutrition and accelerating the catabolic loss of body weight. It causes the conversion of second degree burns to full thickness lesions, thus increasing the severity of the injury and delaying epithelial healing.

Since the ultimate recovery of the severely burned patient coincides with the healing of the burn wound, good care of the wound contributes more to the control of infection and hence to a decrease in mortality and morbidity than any other single factor. The basis of local wound therapy in burns includes thorough cleansing and debridement of the wound, in conjunction with the direct application of antibacterial agents (Boswick and Stone, 1968). It has been shown by morphological studies that antibiotics cannot be brought to the burn wound in sufficient quantities by the systemic route because of the extensive disruption of the vascular supply in the burn area and its immediate vicinity (Order, 1968). As the control of environmental sterility and total isolation of the patient is not usually feasible, even in a large burn centre, let alone in the average general hospital, topical antibacterial agents are, at present, playing a prominent role in the continuing struggle of the surgeon to decrease wound sepsis and invasive infection (Hummel, 1970).

Since the beginning of recorded medical history, various compounds and applications have been applied to the burn wound. In recent years, there has become available an ever increasing list of topical antibacterial agents for the treatment of burns, as well as a host of differences of opinion regarding the advantages and disadvantages of each. Silver sulfadiazine, as a topical agent, was first introduced by Fox in 1967 and has been in use by us for the treatment of burns since 1971. This paper is an attempt to present the results of our observations on the use of this drug since that time.

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MATERIALS

A total of 179 cases of burns treated with silver sulfadiazine was reviewed. This represented the number of cases admitted to the University Hospital, Kuala Lumpur, over a period of 3½ years from May 1971 to November 1974. The Criteriae for admission to the hospital includes all cases of burns involving more than 10% of the body surface area; all cases with involvement of the face, neck, hands and feet; and all cases of deep burns of an extent requiring subsequent skin grafting. Silver sulfadiazine was used as the primary method of topical therapy in the majority of cases. Patients, whose burn wounds were grossly infected at the time of admission, were submitted to a period of Eusol dressing initially before instituting sulfadiazine therapy.

The cases treated were placed into four groups depending on the extent of the burn wound. The age and sex distribution of the patients in each of these four groups are shown in Table I. The majority of the patients were in the paediatric age group (79 cases). 117 patients had burns involving less than 15% of their body surface area. There were 41 cases with burns of 15-30%; 13 cases with burns of 31-50% and 8 patients with extensive involvement of more than 50% of their body surface area.

While the majority of cases were admitted within a few hours after injury, 62 cases (34.6%) were admitted only after a delay of more than 24 hours. These represented cases who had received initial treatment in other hospitals or clinics around the area. In 32 of the cases seen, the wound was observed to be contaminated or infected at the time of admission. Contamination was usually the result of various topical applications smeared on to the wound by the patients themselves. These varied from coconut oil, toothpaste, coffee powder to various native herbs.

METHOD OF TREATMENT

After appropriate resuscitative therapy had been instituted, the burn wound was thoroughly cleansed with cetrimide or chlorhexidine solutions. Blisters were opened and all non viable tissues excised. Silver sulfadiazine cream was then applied as a thick covering layer with the gloved hand. Care was taken that all crevices, skin folds and irregularities of the burn surface was covered with the cream. The

AGE AND SEX DISTRIBUTION OF PATIENTS ACCORDING TO EXTENT OF BURNS

Extent of Burn (% body surface)	Less than 15%		15 - 30%		31 - 50%		More than 50%		Total
Age Groups	M	F	M	F	M	F	M	F	
0 - 10 yr	25	25	13	10	2	2**	1*	1	79
11 - 20 yr	17	11	5	1	1	0	0	3***	38
21 - 30 yr	13	4	6	1	1	1	1	1*	28
31 - 40 yr	4	5	3	0	0	1	0	0	13
41 - 50 yr	8	1	1	0	1	2	0	0	13
51 - 60 yr	0	1	0	0	1	1	0	0	3
61 - 70 yr	1	2	0	0	0	0	0	0	3
71 - 80 yr	0	0	0	0	0	0	0	0	0
81 - 90 yr	0	0	0	1*	0	0	1*	0	2
Total	68	49	28	13	6	7	3	5	179

* deaths.

BACTERIAL FLORA OF BURN WOUNDS

Postburn day	1	7	14	21	28	35	42
Total Cultures:	171	81	62	33	24	16	14
Staphylococcus aureus	12	12	—	—	—	—	—
Streptococci							
Nonhemolytic	2	—	—	—	—	—	—
hemolytic	5	—	—	—	—	—	—
Escherichis coli + coliforms	2	9	5	1	—	—	1
B. Proteus	—	3	3	—	—	—	—
Pseudomonas aeruginosa	—	2	14	8	4	2	—
Candida albicans	—	—	—	—	2	1	1
No growth	150	55	40	24	20	14	1

ANALYSIS OF MORTALITY

No.	Age	Sex	Area of Burns (% body surface)	Time of Death (days after injury)	Clinical Cause of Death	Post-Mortem findings
1.	75	Male	100%	1	Burns shock	Pulmonary oedema Tracheo-bronchial smoke casts cooked viscerae
2.	83	Female	20%	28	Respiratory Failure	Hypostatic pneumonia
3.	2	Female	30%	15	Septicaemia	nil
4.	10	Female	40%	33	Septicaemia	nil
5.	11	Female	56%	1	Cardio-resp. arrest	Laryngeal oedema
6.	19	Female	75%	13	Septicaemia pulmonary oedema	Pulmonary oedema
7.	20	Female	75%	15	Septicaemia	nil
8.	22	Female	90%	1	Burns Shock	Pulmonary oedema

exposure method was generally used for the face, neck, anterior trunk and perineum. While this method entails more frequent application of the ointment, (12 hourly) we have found it advantageous in that it allows us to observe whether infection is developing. However, occlusive dressings are applied over the cream in cases with circumferential burns of the extremities or in restless, uncooperative children.

The wounds were cleansed twice daily and fresh cream reapplied. Repeated debridement was done at the bedside with each dressing change. Tubbing was not usually started until one week after injury, when it was used routinely before each dressing change.

All areas of partial thickness burns were treated conservatively by the above regime. Unless infection had occurred, by the end of the second week, one could usually see islands of regenerating epithelium appearing in the wound. Patients with demarcated full thickness burns were subjected to tangential excision of the eschar as soon as the general condition of the patient was stabilised. Autografts were usually harvested from the uninvolved areas of the body and placed on the wound 24 hours after excision. This procedure was generally confined to cases with full thickness burns of less than 20% of their body surface area. In patients with more extensive deep burns, staged excision and grafting were carried out. Initial skin grafting was done either with the use of autografts if the area to be covered was small and the wound infection controlled, or temporarily with heterografts.

Wound swabs were taken for culture at the time of admission and at weekly intervals thereafter. Blood cultures were taken only if the patient showed evidence of systemic spread of the infection.

RESULTS

There were 8 deaths out of a total of 179 cases giving an overall mortality rate of 4.5%. Of these, 3 could be classified as early deaths, occurring within 48 hours after injury. Two of the early deaths were the result of burn shock in cases of very extensive burns (90% and 100%). The third death was due to cardiopulmonary arrest as a result of undetected laryngeal oedema. The remaining deaths all occurred more than two weeks after injury. One case died as a result of respiratory complications due to prolonged confinement in bed. The other four were attributed to invasive infection and septicaemia. In all these four cases, blood cultures confirmed the presence of Pseudomonas aeruginosa in the blood stream.

No patient with less than 15% burns died. There was only one death in the 15-30% group giving a mortality rate of 2.4%. Out of 13 cases in the 30-50% group, there were 2 deaths and both of these were in patients under 10 years of age, giving a mortality rate of 15.4%. With cases of extensive burns involving more than 50% of the body surface area, the mortality rate rose alarmingly high to 62.5%.

The results of wound cultures showed that there were 21 cases with positive wound infections on the day of admission. A high proportion of these cases were the result of delay in admission. The predominant organisms in these cases were Staphylococcus aureus and streptococci. By the end of the first week after admission, the gram negative bacilli began to make their appearance in the wound cultures. The incidence of Pseudomonas aeruginosa infection showed an increase at the end of the second week and continued to remain as the major infecting organism after that. Candida albicans, which was not cultured from the burn surface during the first three weeks was noticed to be present in 4 patients with severe burns after that period.

In all the cases where silver sulfadiazine was the primary topical agent used, it was noticed that there was no complaint of pain during the application of the cream over either fresh burns or raw granulating surfaces. No heavy sedation or analgesia was needed during dressing changes. On the contrary, its application had a soothing effect by relieving burn pain. Unlike our previous experiences with silver nitrate, there was no staining or discolouration of tissues, dressings or clothing. This has been an important factor in the ready acceptance of silver sulfadiazine by both the patients and nursing personnel. No acid-base abnormality, electrolyte imbalance or methemoglobinemia was observed in any of the cases. While isolated incidences of hypersensitivity reactions have been reported in the literature, no such occurrence has been observed in our patients.

The response of the wound to the application of silver sulfadiazine was impressive. The eschar under the dressings became soft and pliable and gradually disintegrated or could be easily removed. The underlying tissues looked exceptionally healthy and wound smears and cultures rarely showed any growth in most cases. When the occlusive method was used, the dressings did not stick or become adherent even if left for 24-48 hours after application. It was frequently observed that the surface of the cream or the fine mesh gauze over the wound was covered with a yellowish viscuous or crusty exudate. This, however, while showing some leucocytes on staining, contained little or no bacteriae. As the eschar was cleared away, regenerating islands of epithelium became conspicuous. Many burns healed in regions which originally appeared to be full thickness injuries and skin grafting was always less in area than anticipated.

DISCUSSION

The syndrome of 'burn wound sepsis' was first established by Brentano in 1966. He showed that it was due to the rapid proliferation of bacteria in the burn wound with an active invasion of the adjacent

unburned tissues by these microorganisms in numbers exceeding 100,000 per gram of tissue. He demonstrated that it was the gram negative bacilli, predominantly Pseudomonas aeruginosa, which were the primary organisms responsible. These spread initially by way of the lymphatics, but later invade the vascular network as septicaemia occurred (Moncrief, 1964).

Our experience showed that the initial infecting organisms were predominantly staphylococcus and streptococcus. However, there was no case of gram positive septicaemia observed even though it has been observed that the patient is noticeably susceptible to bacterial infection in the period immediately following the infliction of an extensive burn (Alexander and Moncrief, 1967). This susceptibility is due to the loss of protective skin covering; the presence of avascular tissue favouring bacterial growth, as well as an alteration in the normal inflammatory reaction and a decrease in antibody response to antigenic stimuli. This suppression of the body's defence mechanism is usually noted to be over 24-48 hours after injury. However, the four deaths in our series, were due to gram negative septicaemia and occurred between the second and fifth week after injury, with a mean postburn day of death of 19 days. This coincides with the highest incidence of pseudomonas aeruginosa cultured from the burn wounds. This change in the bacteriological flora of the burn wound, from an initial infection by gram positive cocci to gram negative infection during the course of therapy, has been observed by other authors. Conway (1967) noted that when Pseudomonas is present for more than a brief time in a wound, it often becomes the dominant organism, either by directly suppressing other species or by surviving their elimination due to a greater resistance to antimicrobial agents.

While topical antibacterial agents provide only one aspect of treatment for burn wound sepsis and should be considered in relation to all other adjunctive therapeutic procedures, they still form the mainstay of the treatment program in most burn centres. All the topical agents which have been in use in recent years have been effective to some degree in controlling burn wound sepsis. They do not completely eliminate bacteriae from the burn wound but, when properly used, prevent invasive infection. Their main differences revolve around three basic factors; namely, the relative efficacy in controlling or suppressing infection; the presence or absence of side-effects during their use and the effect of the agent on the regeneration of the epidermis.

In our series, despite the fairly high percentage of positive wound cultures, we had only 4 cases of septicaemic deaths, giving a mortality rate due to sepsis of only 2.2%. Our observations on the efficiency of silver sulfadiazine has been confirmed by the combined experiences of many burn therapists in other countries. In addition to the advantages mentioned, the other factors contributing to the acceptibility of this agent include:—

1. Its potent bactericidal activity against a wide range of organisms such as B. proteus, Klebsiella, Staphylococci, Candida and Pseudomonas. The minimum inhibitory concentration against these organisms is 25-100 times less than that of sulfamylon acetate or the sulfonamides. Unlike the sulfonamides, it is not inhibited by paraamino benzoic acid. The levels of the drug in the wound exudate 24 hour after application ranged from 40 to 95 mg% and represented a satisfactory reservoir of antibacterial activity even at that dilution (Fox, 1968).
2. Only 10% or less of the sulfonamide moiety is absorbed and absorption is less during the immediate postburn period. The levels of sulfonamide in the blood and urine in 357 samples investigated by Fox (1968) were consistently low. No instance of renal toxicity has been described, nor would any be expected at these low concentrations.
3. The silver ions from the material is not absorbed from the burn wound, in contrast to the detection of 5-30 ug% in the plasma of patients after silver nitrate soaks. (Monafo, 1968). These ions however, have been found to combine with sulfhydryl groups and proteins, including bacterial DNA and RNA. This may account for the potent inhibition of bacterial growth achieved by silver sulfadiazine (Fox, 1970).
4. The drug does not inhibit the action of proteolytic enzymes or collagenase. These are normally responsible for autolysing necrotic tissues. Hence separation of the eschar is not delayed (Hummel, 1970).
5. Unlike silver nitrate and sulfamylon acetate, which resulted in inhibition of epithelial regeneration, no such effect was observed with silver sulfadiazine (Scapicchio, 1968).

CONCLUSION

Silver sulfadiazine, introduced by Fox about 7 years ago, has been responsible for an increase in the efficiency of topical burn therapy. The low incidence of positive wound cultures, reduced mortality rate from sepsis, in addition to its convenience of use as well as an almost total absence of side effects, has made it widely acceptable as a topical agent for the control of burn wound sepsis.

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