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A new povidone-iodine cream for the treatment of burns

Comparison with a standard topical regimen

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Summary

A remarkable improvement in the rate of burn healing has been achieved with a mixture of povidone-iodine ointment (Betadine) and malic, benzoic and salicylic acids (MBS) (Aserbine). A study was undertaken to compare the effects of a new povidone-iodine formulation (Betadine cream) with and without MBS with povidone-iodine ointment plus MBS. All preparations were easy to apply and were readily removed, causing only mild discomfort on application in the majority of cases.

A significant difference in healing times was observed between povidone-iodine cream and

povidone-iodine cream plus MBS. There was also a significant difference in the decrease in the number of positive bacterial cultures between these two treatments. This applied to both superficial and deep burns. No skin sensitivity reactions were reported with any of the preparations.

The addition of MBS to povidone-iodine cream did not produce as significant an improvement in results as its addition to povidone-iodine ointment.

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Much progress has been made in the last 15 years in the management of patients with burns, especially in the treatment of shock. Infection caused by the proliferation of pathogenic organisms, chiefly bacteria and fungi, is the foremost problem in treatment. It is important, therefore, to search for locally applicable preparations capable of effectively disinfecting the surface of the burnt area. The principal requirements of such a preparation are that it is non-irritant, easily applied (i.e. spreads well) and is without effect on acid-base balance.

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Povidone-iodine (Betadine) is as effective a disinfectant as iodine alone and is non-irritant. It has been used successfully in the treatment of burns and wounds.¹⁻⁴ In patch tests carried out on 6000 patients with contact dermatitis only 3 were found to be allergic to povidone-iodine. As an iodophor, povidone-iodine slowly liberates iodine when in contact with the skin or mucous membranes. It is active against both Gram-negative and Gram-positive bacteria, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella* species. Povidone-iodine also possesses very marked antimycotic activity and is one of the few preparations really effective against *Candida albicans*.²

The combination of malic, benzoic and salicylic (MBS) acids (Aserbine) is water-soluble and is available as a cream or a solution; it breaks down necrotic tissue.

In a previous study,¹ a remarkable improvement in the rate of burn healing was achieved with a mixture of povidone-iodine ointment and MBS. It was postulated that MBS breaks down the necrotic tissue thus allowing povidone-iodine ointment to penetrate to the depths of the wound. In this manner, control of sepsis would be far more effective than

merely applying the ointment or necrolytic cream to the surface of the burn.

Povidone-iodine cream was developed to incorporate the properties of easy spreading and comfortable application to ensure maximum comfort for the patient while retaining its essential antibacterial properties.

A study was designed to assess the safety and efficacy of a povidone-iodine cream, with and without the addition of MBS, compared with the efficacy of povidone-iodine ointment with MBS.

Patients and methods

The study population included patients of all races (adults and children) with 'fresh' burns admitted to the Burns Unit at Tygerberg Hospital over a 9-month period. The nature of the investigation was fully explained to each patient (or to the parents of child patients) and verbal informed consent was obtained. If not, patients were excluded from the trial. Concurrent medication was noted.

TABLE I. THE VARIABLES — DISTRIBUTION PER GROUP

	Povidone-iodine cream	Povidone-iodine cream plus MBS	Povidone-iodine ointment plus MBS
Average age (yrs)	19,4 ± 18,0	18,0 ± 19,0	17,4 ± 17,3
Distribution of burn(s) (%TBSA)			
0-10	4	12	8
11-20	10	7	13
21-30	6	4	3
31-40	3	0	—
41-50	1	1	—
51-60	1	1	—
60+	—	—	1
Average burn size per group (% TBSA)	14,4 ± 17,5	13,90 ± 12,3	13,5 ± 15,2
Burn type			
Fluid	15	15	16
Flame	9	8	6
Chemical	—	—	2
Electrical	—	—	1
Fluid and flame	1	2	—
Area involved			
Head and neck	11	14	14
Trunk	18	16	19
Arm	15	10	10
Hand	7	2	3
Leg	9	7	3
Foot	5	1	2
Perineum	2	1	0
Debridement and skin grafting			
Superficial (%TBSA)			
0-10	6	4	6
11-20	5	1	3
21-30	—	—	—
31+	—	—	—
Deep (%TBSA)			
0-10	9	3	9
11-20	3	1	1
21-30	—	1	—
31-40	1	1	—
41-50	—	—	—
51-60	—	—	1

Three successive groups each of 25 patients with fresh burns were allocated to undergo topical treatment with povidone-iodine cream, povidone-iodine cream plus MBS or povidone-iodine ointment plus MBS. The patients in each group were comparable for age, size and depth and distribution of burn.

Assessment

The povidone-iodine cream with MBS and povidone-iodine ointment with MBS were mixed in equal parts in a sterile container immediately before use and the appropriate combination was smeared onto sterile gauze dressings with a sterile applicator. The dressings were then applied over the burnt area(s).

On admission all patients had a full medical history recorded. A complete examination was undertaken. The extent, site of the burn(s) and whether superficial or deep was recorded. The cause of the burn(s) was also established. Operative procedures such as debridement of skin and skin grafting were noted. When necessary, analgesics were given and intravenous fluids administered.

During application of the medication to superficial burn(s) a record was kept of: (i) the degree of pain experienced (mild, moderate or severe); (ii) the ease of spread of the preparations (excellent, satisfactory or poor); and (iii) the removal of the dressing (easy or difficult).

The respective topical burn treatment was reapplied daily until the wound had healed or was ready for skin grafting.

If antibiotics were required during the study this was recorded. The decision to give antibiotics was based on bacterial culture and sensitivity.

The following were checked daily: (i) temperature; (ii) general condition of the patient, including hydration; (iii) the patient's mental state; (iv) the degree of wound healing — the wound edge was inspected for evidence of cellulitis, healing was defined as complete epithelialization of the burnt area, and the rate of wound healing for both deep and superficial burns was recorded; and (v) evidence of systemic infection, e.g. septicaemia or abscess formation at distal sites; any other medical complications were also recorded.

Bacterial swabs were taken from the burn surface weekly and the cultured organisms identified.

Results

The groups were comparable for age, distribution of burn(s), average burn size and burn type (Table I). The range of ages in each group were: povidone-iodine cream — 5 weeks - 64 years; povidone-iodine cream plus MBS — 1 - 65 years; povidone-iodine ointment plus MBS — 6 months - 53 years. To determine the distribution of burns in a group, the total percentage of burnt

body surface area per patient was calculated and this was classified. The average burn size per classification (percentage total body surface area; %TBSA) in all patients per group was calculated, and an overall average for each group reached. The distribution per group of patients who underwent debridement and skin grafting is also shown in Table I.

All three preparations were easy to apply and to remove, causing mild discomfort on application in the majority of cases (results not shown). After the first week between 96% and 100% of patients experienced mild-to-moderate pain upon application of any of the three preparations. The spreading ability of the cream, the cream plus MBS and the ointment plus MBS was 'excellent' in 92%, 88% and 100% of patients respectively (results not shown). Removal of the dressing was 'easy' in 100% of patients with the cream, 92% with the cream plus MBS and 100% with the ointment plus MBS (results not shown).

Statistically significant differences were observed in healing times (Table II). The number of days to complete wound healing was calculated from the day of injury. There was a statistically significant difference ($P < 0,001$, two-tailed t -test) between the mean number of days for complete wound healing in patients with superficial burns of 0-10% treated with povidone-iodine cream and those treated with povidone-iodine cream plus MBS, the latter healing significantly faster. No other statistical differences were found for superficial wounds (Table III) because of the large standard deviations observed.

Deep burns covering 0-10% TBSA treated with povidone-iodine cream plus MBS healed significantly faster ($P < 0,01$, two-tailed t -test) than those treated with povidone-iodine cream or povidone-iodine ointment plus MBS. Deep burns involving 31-40% TBSA treated with povidone-iodine cream with or without MBS healed within 34-35 days, approximately the same healing time (39 days) for deep burns of lesser surface area (11-20%) treated with povidone-iodine ointment plus MBS. No statistical analysis is possible because of the small number of patients involved in each group.

Swabs were taken once a week from the burn surface, and the bacteria cultured and identified. The figures in Table III represent the number of times a particular species of bacterium was isolated, regardless of whether it had been isolated from that patient before. In order to test for statistical significance the total number of bacteria isolated up to 4 weeks after injury per group was calculated. There was a marked decrease in the total number of times *Staphylococcus* and *Pseudomonas* species of bacteria were recorded in burns treated with povidone-iodine cream with or without MBS compared with those treated with povidone-iodine ointment plus MBS (Table III).

The total number of bacteria cultured from wounds treated with povidone-iodine cream plus MBS was the lowest of the three preparations. There was a statistically significant difference between

TABLE II. WOUND HEALING (DAYS)

%TBSA	Povidone-iodine cream	Povidone-iodine cream plus MBS	Povidone-iodine ointment plus MBS
Superficial			
0-10	20,5 ± 7,7 (11)*	11,8 ± 8,2 (18)	18,7 ± 10,0 (17)
11-20	24,4 ± 6,0 (18)	22,7 ± 11,2 (3)	33,0 ± 22,3 (5)
21-30	—	—	—
31+	—	—	—
Deep			
0-10	22,3 ± 7,3 (15)**	13,7 ± 7,5 (8)**	24,7 ± 9,9 (13)
11-20	23,7 ± 8,6 (4)	33,0 (1)	39,0 (1)
21-30	—	41,0 (1)	—
31-40	34,0 (1)	35,0 (1)	—
41-50	—	—	—
51-60	—	—	66,0 (1)

* $P < 0,001$.

** $P < 0,01$.

Deep burns — total healing time = time to last skin grafts plus 5 days.

Figures in brackets show number of patients in group.

TABLE III. BACTERIOLOGY

Organism	Povidone-iodine cream	Povidone-iodine cream plus MBS	Povidone-iodine ointment plus MBS
<i>Staphylococcus</i> spp.	16	8	56
<i>Pseudomonas</i> spp.	8	6	17
<i>Streptococcus</i> spp.	6	3	5
<i>E. coli</i>	—	—	1
<i>Proteus</i>	4	—	1
<i>Acinetobacter anitratus</i>	1	1	1
<i>Enterobacter cloacae</i>	1	1	—
<i>Serratia marcescens</i>	—	1	—
<i>Klebsiella</i> spp.	1	1	—
<i>Clostridia</i>	1	—	—
Total	38	21	81

$P < 0,01$ $P < 0,001$ $P < 0,001$

TABLE IV. COMPLICATIONS

	Povidone-iodine cream	Povidone-iodine cream plus MBS	Povidone-iodine ointment plus MBS
Pyrexia	3	2	2
Dehydration	—	1	—
Mental confusion	2	1	—
Cellulitis	—	—	—
Septicaemia	1	2	—
Metastatic abscess	—	—	—
Hyponatraemia	3	1	1
Hypernatraemia	1	—	—
Pulmonary involvement	4	2	1
Convulsions	1	—	—

the total number of times bacteria were isolated cumulatively after 4 weeks from patients treated with povidone-iodine cream plus MBS ($P < 0,001$; chi-square test) or without MBS ($P < 0,001$; chi-square test) and those treated with povidone-iodine ointment and MBS (Table III).

No skin-sensitivity reactions were reported, and no serious complications could be ascribed to any of the three preparations (Table IV).

Discussion

The principal disadvantages of many topical burn medications are: (i) reported absorption of toxic ingredients; (ii) frequency of allergic reactions; (iii) severe pain on application; (iv) a growing resistance to locally applied antibiotics; and (v) difficulty of removal and hindrance to visual observation in judging the progress of the wound.

The ointment contains as its active ingredient 10% povidone-iodine (1% available iodine), and possesses the broad microbiological properties of iodine which are lethal to Gram-positive and Gram-negative bacteria, fungi, yeasts, viruses and protozoa.⁵⁻⁷ There is no reported tissue irritation or staining such as is associated with elemental iodine administration. It is effective against antibiotic-resistant organisms,⁷⁻⁸ and no resistance of strains to the preparation has been reported.

The povidone-iodine cream was primarily developed as a topical burn preparation which would be easy to apply, would cause the patient minimal discomfort and be easy to remove

for visualization of the wound. The cream would result in a soft, more pliable type of crust which would allow easier movement by the patient without the tendency to crack over the flexor surfaces. Previous studies comparing ointment bases and creams suggest that the vehicle may enhance drug penetration in one or more ways, e.g. by ensuring good contact with the body surface. In a series of experiments to show the influence of the vehicle on the bio-availability of four corticoids under various galenical forms, such as fatty ointments or water in oil (w/o) and oil in water (o/w) creams, the emulsified forms were the most efficient formulations. The o/w cream was the best delivery system tested.⁹ Creams are easier to apply and remove and hence are less likely to damage newly formed tissues; they are also more soothing. O/w creams (povidone-iodine cream) mix with discharges and are particularly suitable for weeping or wounded surfaces. They allow some perspiration and heat to escape, and the cooling caused by evaporation of the continuous phase is soothing.

The efficacy of povidone-iodine ointment plus MBS has already been established.¹ It was important to study the efficacy of the new cream form, with and without MBS, compared with the highly effective combination of povidone-iodine ointment plus MBS.

The results from this study show that the cream with or without MBS is as easy to apply and remove as the ointment plus MBS. With povidone-iodine cream there is as good, and in some instances better, healing of burns as with povidone-iodine ointment plus MBS. However, the addition of a necro-

lytic cream to povidone-iodine cream does have favourable effects on wound healing and bacterial counts. More importantly this study suggests that povidone-iodine cream can penetrate the wound more effectively than the povidone-iodine ointment plus MBS combination, although the addition of a necrolytic cream is still beneficial (Tables II and III). However, for practical purposes the application of the cream is far less time-consuming than mixing the cream with the necrolytic agent before application.

The decrease in positive bacterial cultures with application of the povidone-iodine cream compared with povidone-iodine ointment plus MBS indicates that the cream may penetrate better than the ointment mixture. An occlusive layer of a medicated dermatological product may, by reducing evaporation of water from the skin into the atmosphere, increase hydration of the horny layer of the skin and therefore promote penetration of the medicament.

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Effects of an oats fibre tablet and wheat bran in healthy volunteers

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Summary

The daily intake of total dietary fibre of a group of 18 healthy volunteers was raised from a mean of 22,1 g to 32 g by supplementing their diet with either 23 g wheat bran or 15 g oats fibre tablets in a cross-over design for two 3-week periods with a wash-out period of 4 weeks in between. Both fibre supplements improved mean glucose tolerance, although not significantly. During the first period, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol were significantly lowered by both fibre preparations. During the second period significant reductions in TC and LDL-C were obtained only in the group taking the oats fibre tablets. This could probably be explained as an effect of the gel-forming fibre components in oats fibre. High-density lipoprotein cholesterol concentrations remained unchanged. The oats fibre tablet also proved easier to take and caused fewer side-effects. This study shows that if dietary fibre concentrates are used to increase fibre intake in Western societies,

better results will probably be obtained by using a dietary fibre concentrate or mixture of concentrates that contain both soluble and insoluble components.

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There have been several recommendations during the past few years that the dietary fibre intakes of Western societies should be increased,¹⁻⁴ based on epidemiological evidence that dietary fibre protects against diseases such as constipation, diverticular disease, coronary heart disease, diabetes mellitus and some cancers.^{5,6} Excellent results have also been obtained by treating patients with diabetes mellitus with high-fibre diets,^{7,8} and experimental evidence has shown that certain dietary fibre components improve serum lipid profiles.⁹

High-fibre diets are, however, not always acceptable to everyone, perhaps because of ingrained eating habits, lack of palatability, large volumes and possible side-effects such as fullness, a bloated feeling and increased flatus production. A solution could be to use dietary fibre concentrates or isolates as supplements. Wheat bran is a readily available and inexpensive fibre concentrate, generally used to treat constipation.¹⁰ Although an increased intake protects against constipation and related diseases,¹⁰ there have been reports that wheat bran does not influence serum lipids.^{11,12} Another problem is that some subjects, especially those with ulcerative colitis and mild gluten sensitivity, cannot tolerate wheat bran in sufficient quantities to experience its beneficial effects. Cereal fibre from oats (*Avena sativa* or *byzantina*) has been reported to improve serum lipid values of hypercholesterolaemic men.¹³

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