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Topical antibiotics in the treatment of superficial skin infections in general practice—a comparison of mupirocin with sodium fusidate

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Summary

A total of 413 eligible patients took part in an observer-blind randomised multicentre clinical trial in order to compare the clinical and bacteriological efficacy of mupirocin (Bactroban) ointment with sodium fusidate (Fucidin) ointment for treating superficial skin infections seen in general practice. Mupirocin was applied twice daily and sodium fusidate thrice daily for a period of 7 days. Both treatments were similarly effective with 97% patients treated with mupirocin and 93% patients treated with sodium fusidate responding. Mupirocin was significantly more effective in the treatment of acute primary skin infections and in the treatment of a subgroup of patients with impetigo ($P < 0.01$). Of the organisms detected before treatment began, 93% were not found after treatment with mupirocin compared with 89% after treatment with sodium fusidate. *Staphylococcus aureus* and/or β-haemolytic streptococci appeared to be eliminated in significantly more patients treated with mupirocin (96%) compared with those treated with sodium fusidate (88%), ($P = 0.03$). Both treatments were well tolerated.

Introduction

Mupirocin 2% in a polyethylene glycol base (Bactroban®) is a novel topical antibiotic for treating bacterial skin infections. It is active against Gram-positive and some Gram-negative organisms.[1–3] Sodium fusidate 2% in an ointment base (Fucidin®) has a similar range of activity.[4]

Trials have shown that the clinical efficacy of mupirocin in the treatment of skin infections compares favourably with orally administered antibiotics such as erythromycin,[5–7] cloxacillin,[5,6] or flucloxacillin.[7]

Previous comparative studies against topical antibiotics have shown that mupirocin is as effective in the treatment of skin infections as chlortetracycline[8,9] gentamicin,[10] neomycin[11] and fusidic acid.[12] This study compared the clinical and bacteriological efficacy and tolerance of mupirocin with sodium fusidate in patients with various skin infections seen in general practice.

Patients and methods

Design of the study

From 1985 to 1987, 21 general practitioners in the U.K. recruited patients for the study. Any patient with a primary or secondary skin infection, other than

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a leg ulcer, suitable for treatment with a topical antibiotic was eligible for entry. Patients were excluded if they had received topical or systemic antibiotics within the previous 72 h, were diabetic or were known to be allergic to mupirocin or sodium fusidate. Informed consent was obtained and patients were randomised to receive treatment with either mupirocin or sodium fusidate. For this purpose, a code was designed in blocks of six so that twice the number of patients at each centre received mupirocin than received sodium fusidate. Four plain tubes containing the preparations were supplied for each patient. These were labelled with instructions for use but the name of the antibiotic was omitted. Mupirocin was to be applied twice daily and sodium fusidate thrice daily, each for a period of 7 days. The tubes were supplied in a sealed box labelled only with the patient's number. Thereby, the observer did not know which antibiotic a patient was receiving. Patients were requested to return for assessment 3 or 4 days after starting treatment and again 3 or 4 days after treatment ended.

Clinical assessments

At entry to the study, the type and severity of infection and the degree of itching and stinging was recorded. At each following visit, a further assessment was made of the severity of the infection and the patient was asked 'Does the treatment suit you?' Clinical efficacy was assessed as healed, improved, unchanged, worse or failed. (Withdrawal from the study for a change of antibiotic therapy was classed as a failure.) Patients with a healed or improved lesion at the end of the study were classed as having a successful outcome.

Bacteriological assessments

Swabs taken before and after treatment were sent in transport medium by first class post to one central laboratory. The swabs were inoculated onto a range of microbiological culture media which were incubated at 37 °C under various atmospheric conditions. Routine methods of bacterial identification were used. Antibiotic susceptibility tests were performed by means of a modified Stokes' disc method on Isosensitest agar containing 0·5 % saponin-lysed horse blood, except for streptococci when blood agar was used. Discs contained 5 mcg mupirocin for Gram-positive organisms, 200 mcg mupirocin for Gram-negative organisms and 10 mcg fusidic acid for both Gram-positive and Gram-negative organisms.

Minimal inhibitory concentrations (MIC) of mupirocin and fusidic acid were determined for *Staphylococcus aureus* and β-haemolytic streptococci by an agar dilution method. The medium used was Diagnostic Sensitivity Test Agar (Oxoid) supplemented with 5 % saponin-lysed horse blood. The plates were inoculated by means of a multipoint inoculator (Denley) with a dilution of an overnight culture in Brain Heart Infusion broth so as to give an inoculum of approximately 5×10^3 colony forming units per spot. If pathogens were still isolated after treatment, MICs were determined on the pre- and post-treatment isolates in most cases.

Bacteriological efficacy was assessed in two ways: (1) reduction in the number of organisms found before treatment; (2) the number of patients from whom pathogens were seemingly eliminated (a successful bacteriological

outcome). A pathogen was defined as an organism generally accepted as being a causative agent in skin infections, e.g. a β-haemolytic streptococcus or *S. aureus*. Other organisms, such as coliforms, were regarded as being unlikely causative agents in skin infections.

Statistical analysis

The proportions of patients with a successful outcome (clinical or bacteriological) in the two treatment groups were compared by use of the χ^2 test with Yate's correction (χ^2_c) as appropriate.

Results

Patients

Altogether, 413 patients were eligible for entry to the study. Of these, 275 received mupirocin and 138 received sodium fusidate. A total of 23 patients (12 treated with mupirocin and 11 treated with sodium fusidate) could not be clinically assessed for the following reasons: failure to attend for assessment (eight and three, respectively); withdrawal due to a revised diagnosis (one and one, respectively); prescription of antibiotics for reasons other than lack of efficacy (three and two, respectively); non-compliance (nil and four, respectively); inadequate data (nil and one, respectively). Thus, 390 patients remained for evaluation of efficacy. All patients, however, were included in the analysis of tolerance.

The two groups were comparable with regard to age, sex and race. The patients' ages ranged from 11 months to 84 years.

Withdrawals

Eighteen patients were withdrawn from the study: 7 (2·5%) in the mupirocin group and 11 (8·0%) in the sodium fusidate group. There were significantly fewer withdrawals in the mupirocin group ($\chi^2 = 6{\cdot}5$, 1 d.f., $P = 0{\cdot}01$). The difference between the groups was largely accounted for by the number of patients withdrawn due to lack of efficacy, being 1 and 5 respectively. Other reasons for withdrawal were adverse events (2 and 2), revised diagnosis (1 and 1), antibiotics administered for reasons other than lack of efficacy (3 and 1) and non-compliance (0 and 2).

Types of skin infections

Skin infections were classified into four main categories; they were further specified whenever possible. Of all the patients, 59% had a primary skin infection; most (40% of all patients) had impetigo. An infected dermatosis afflicted 10% patients, infected eczema being the most common, while 26% patients had infected traumatic lesions. The remaining 5% had various other infections, e.g. secondarily infected viral or fungal lesions. There was a similar distribution of type and severity of infection between the two treatment groups.

Table I *Clinical outcome*

Type of skin lesion	Healed	Improved	Unchanged Failed Worse	Clinical success (healed + improved, %)
	Mupirocin, no. of patients ($n = 263$)			
Primary infection (impetigo)	116 (81)	38 (24)	3 (1)	98 %* (99 %)**
Infected dermatosis (eczema)	14 (11)	9 (8)	2 (2)	92 % (90 %)
Infected traumatic lesion	40	30	3	96 %
Other	3	5	0	100 %
Total	173	82	8	97 %
	Sodium fusidate, no. of patients ($n = 127$)			
Primary infection (impetigo)	50 (33)	17 (10)	7 (6)	91 %* (88 %)**
Infected dermatosis (eczema)	11 (9)	3 (2)	1 (1)	93 % (92 %)
Infected traumatic lesion	15	15	0	100 %
Other	6	1	1	88 %
Total	82	36	9	93 %

* $\chi^2 = 6{\cdot}9$, 1 d.f., $P < 0{\cdot}01$. ** $\chi^2_c = 7{\cdot}5$, 1 d.f., $P < 0{\cdot}01$.

Clinical efficacy

Of the patients who attended for their first subsequent visit, 2, 3 or 4 days after the start of treatment, the condition in 91 % (176) treated with mupirocin was healed (11 %) or improved (80 %) compared with 87 % (82) treated with sodium fusidate whose condition was healed (11 %) or improved (76 %).

The final clinical outcome of the patients in the two treatment groups is shown in Table I. Both treatments were similarly effective with 97 % of the mupirocin group and 93 % of the sodium fusidate group having a successful clinical outcome.

In the treatment of primary skin infection, however, 98 % patients in the mupirocin group and 91 % in the sodium fusidate group had clinically successful outcomes ($\chi^2 = 6{\cdot}9$, 1 d.f., $P < 0{\cdot}01$). In the subgroup of patients with impetigo, 99 % of those treated with mupirocin and 88 % of those treated with sodium fusidate had a clinically successful outcome ($\chi^2_c = 7{\cdot}5$, 1 d.f., $P < 0{\cdot}01$).

Eight patients (3 %) failed to respond clinically to mupirocin treatment. Their diagnoses were impetigo (1), staphylococcal lesion (1), infected eczema

Table II *Apparent elimination of organisms isolated from pre-treatment cultures of bacteriologically evaluable patients*

	Treatment group			
	Mupirocin		Sodium fusidate	
Organism isolated	'Eliminated'	Not 'eliminated'	'Eliminated'	Not 'eliminated'
Staphylococcus aureus	112 (97%)	4	46 (90%)	5
β-Haemolytic streptococci	38 (100%)	0	9 (75%)	3
Coliforms	19	7	9	1
Staphylococcus epidermidis	4	0	3	0
Pseudomonas sp.	1	1	1	0
Proteus sp.	1	0	2	0
Bacillus sp.	1	0	0	0
Coryneforms	1	0	1	0
Other streptococci	2	0	1	0
Candida sp.	2	1	0	0
Total	181	13	72	9
	93% 'eliminated'		89% 'eliminated'	

(2), infected traumatic lesions (3) and an infected sebaceous cyst (1). In seven cases, either pathogens were not isolated from pre-treatment swabs or they were apparently eliminated. One patient with infected eczema still had *S. aureus* present when withdrawn from the study after only 4 days of treatment.

Nine patients (7%) failed to respond clinically to treatment with sodium fusidate. Their diagnoses were impetigo (6), infected groin lesion (1), infected eczema (1) and infected nappy rash (1). In six cases either pathogens were not isolated from pre-treatment swabs or they were apparently eliminated. A follow-up swab was not available in one case (impetigo); a follow-up swab of the nappy rash in another case grew *Candida* sp. and in one case of impetigo a β-haemolytic streptococcus persisted at the end of the study.

Bacteriological efficacy

The bacteriological outcome was considered for the 390 clinically evaluable patients. The pre-treatment swabs from 129 (33%) patients did not yield significant growth of bacteria. From the remaining 261 patients, 323 strains of organisms were isolated before treatment began. Of these patients, 43 could not be evaluated bacteriologically because follow-up swabs were not taken, mainly because the lesion had healed. The organisms most commonly isolated were *S. aureus* (64%) and β-haemolytic streptococci (18%).

In the mupirocin group, 93% of the organisms were apparently eliminated compared with 89% in the sodium fusidate group (Table II). A higher percentage of both *S. aureus* and β-haemolytic streptococci appeared to be eradicated in the mupirocin group compared with the sodium fusidate group. In several cases more than one species of organism was isolated from a single

Table III *Bacteriological outcome*

Patients	No. of patients treated with: Mupirocin	Sodium fusidate
	Bacteriologically evaluable	
Pathogens pre-treatment	130	56
'Eliminated'	125 (96%)*	49 (88%)*
Not 'eliminated'	5	7
Pre-treatment organisms of unlikely significance	20	12
	Bacteriologically unevaluable	
No growth/normal skin flora pre-treatment	85	44
Follow-up swab not obtained	28	15
Total	263	127

* $\chi^2 = 4{\cdot}86$, 1 d.f., $P = 0{\cdot}03$.

swab. In 36 patients, pre-treatment swabs yielded both *S. aureus* and β-haemolytic streptococci; 18 of them had a clinical diagnosis of impetigo.

Pathogens were apparently eliminated in 96% of the mupirocin treated patients compared with 88% of the sodium fusidate treated patients ($\chi^2 = 4{\cdot}86$, 1 d.f., $P = 0{\cdot}03$) (Table III).

Of the five patients treated with mupirocin and classified as bacteriological failures, four had *S. aureus* present and one β-haemolytic streptococci. With the exception of the one patient with infected eczema (*S. aureus*) who was withdrawn after 4 days, all had clinically successful outcomes. Seven patients were bacteriological failures in the sodium fusidate group; five had persistent *S. aureus* (together with *Streptococcus pyogenes* in one case) and two patients had persistent *S. pyogenes*. All patients had clinically successful outcomes except for one with *S. pyogenes* isolated from impetigo and who remained clinically unchanged. The MIC of mupirocin and fusidic acid was determined for 130 strains of *S. aureus* and 32 strains of β-haemolytic streptococci isolated before treatment began as well as most strains of these pathogens isolated after treatment.

The MIC of mupirocin for *S. aureus* was $\leqslant 0{\cdot}25$ mg/l for all strains tested but there was a bimodal distribution of fusidic acid MIC, being $\leqslant 0{\cdot}5$ mg/l in 97% and 4–8 mg/l in 3% strains. The latter showed reduced sensitivity by disc diffusion testing.

The MIC of mupirocin for *Streptococcus pyogenes* (25 strains) was $< 0{\cdot}06$ mg/l and for other β-haemolytic streptococci (seven strains) 0·06–0·25 mg/l. The MIC of sodium fusidate for *S. pyogenes* was 2–4 mg/l and for other β-haemolytic streptococci 2–8 mg/l. Discrepancies between disc diffusion and MIC results arose when fusidic acid MICs were equal to 4 mg/l.

Mupirocin resistant strains of *S. aureus* and β-haemolytic streptococci were not isolated either before or after treatment. A correlation was not seen between pre- or post-treatment MIC and failure to eradicate the pathogen.

Adverse events

Adverse events were reported for ten patients. Eight patients (six having mupirocin, two having sodium fusidate) reported minor itching, stinging or burning sensations. Seven of these patients, however, had reported similar symptoms on entry to the study; one noted stinging after treatment with mupirocin. One patient died due to a pre-existing gastric carcinoma and one had lymphadenopathy thought to be related to an intercurrent infection. Both of them were in the sodium fusidate group.

Discussion

This study demonstrates that both mupirocin and sodium fusidate are effective in the topical treatment of superficial skin infections seen in general practice and that both medications are well tolerated. Eleven per cent of patients had healed lesions by the fourth day of treatment. At the end of the study both treatments demonstrated similar efficacy. Mupirocin, however, was significantly more successful than sodium fusidate in the treatment of primary skin infections, including impetigo ($P < 0{\cdot}01$). The assessment of bacteriological efficacy of topical antibiotics for treating superficial skin infections is complicated. The main problem is assessment of the clinical significance of bacteria isolated. *S. aureus*, the commonest organism isolated from primary skin infections is a normal commensal of the skin; the role of coliforms in some infections is unclear. Assessment is difficult when there is a good clinical response but failure to eradicate one of several potential pathogens present before treatment. Other problems include (a) the relevance of *in vitro* susceptibility testing to topical agents present in very high local concentrations and (b) the absence of post-treatment swabs from healed lesions.

The 'eradication' rates for organisms isolated before treatment were compared, but for more meaningful results the 'eradication' rates for pathogens (*S. aureus* and β-haemolytic streptococci) isolated from patients were assessed also. The overall rate of 'eradication' of pre-treatment organisms in both groups was similar but mupirocin 'eradicated' pathogens in significantly more patients than did sodium fusidate.

The risks of resistance developing to various antibiotics, including fusidic acid, during topical treatment are well known.[13–16] Resistance to mupirocin among strains of *S. aureus* has been recently reported. Low-level resistance (up to 40 mg/l) may be achieved in the laboratory[17] and has been demonstrated *in vivo*;[18–20] high-level resistance (> 700 mg/l) is reported to be uncommon, relatively unstable and has been associated with prolonged mupirocin treatment.[21,22] The clinical significance of low-level resistance is uncertain in the context of the high concentration of mupirocin achieved by topical application. During this study, in which topical therapy was used for 7 days, no strain of *S. aureus* resistant to mupirocin was detected either by disc diffusion methods or MIC determination.

Development of resistance to fusidic acid following topical treatment is important because it compromises the efficacy of fusidic acid administered systemically for treating severe staphylococcal infections. In contrast,

mupirocin has the advantage that, since it is unsuitable for systemic administration, its topical use cannot influence subsequent systemic treatment of severe infections.

Mupirocin is the first novel topical antibiotic to have been introduced in more than 20 years. The clinical benefit derived from the use of mupirocin was obtained at a cost of £3.55 per 15 g tube of Bactroban® ointment. This compared favourably with the equivalent sized tube of Fucidin® ointment at £2.40.[23]

The results of this study demonstrate that mupirocin is effective and well-tolerated for treating acute bacterial skin infections as seen in general practice, particularly staphylococcal and streptococcal infections.

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