A comparison of the efficacy and safety of mupirocin cream and cephalexin in the treatment of secondarily infected eczema

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Summary

The efficacy and safety of mupirocin calcium cream were compared with those of oral cephalexin in the treatment of secondarily infected eczema. In this multicentre, double-blind, double-dummy study, 159 patients with secondarily infected eczema (suitable for treatment with topical antimicrobials) and a total skin infection rating scale score of 8 or more were randomized to receive either topical mupirocin cream three times daily or oral cephalexin, 250 mg four times daily, for 10 days (intent-to-treat group). Clinical success (per-protocol group), defined in part as a patient with a response of improvement in the skin infection rating scale, was similar in the two groups: 89% for mupirocin ($n = 44$) and 82% for cephalexin ($n = 38$) [$P = 0.29$; 95% confidence interval (−8.4%, 22.5%)]. Bacteriological success (intent-to-treat group), defined as a patient with a response of eradication, improvement or colonization of bacteria at the end of therapy, however, was significantly higher for mupirocin [50% and 28% in the mupirocin ($n = 48$) and cephalexin ($n = 47$) groups, respectively; $P = 0.005$]. Mupirocin cream was as well tolerated as cephalexin; 9% and 13% of patients reported adverse events related or possibly related to study medication in the mupirocin and cephalexin groups, respectively. The most common adverse events overall were diarrhoea and nausea. Mupirocin cream applied three times daily is as effective clinically and superior bacteriologically compared with oral cephalexin given four times daily in the treatment of secondarily infected eczema of limited depth and severity. Mupirocin cream is as well tolerated as oral cephalexin, and more patients prefer the topical regimen, which should improve patient compliance.

Introduction

Bacterial infection is believed to play a role in the clinical expression of many forms of eczema, and significant improvements can sometimes be achieved by the use of topical or systemic antimicrobials. Bacteria are universally present on skin showing eczema, and there is clinical evidence suggesting that bacterial colonization can exacerbate the underlying condition, resulting in frank secondary infection.[1–3] Once it has been determined that there is an infectious component to a patient's eczema, a treatment regimen must be selected that has a high likelihood of resolving the infection while being well tolerated by the patient.

Patients with secondarily infected eczema can be treated with either oral antimicrobials (such as penicillins, cephalosporins, macrolides or fluoroquinolones) or topical antimicrobials, sometimes in combination with anti-inflammatory agents. Topical antimicrobials are preferable in theory to oral antimicrobials because the potential for systemic side-effects (such as abdominal cramping and diarrhoea) and increased antimicrobial resistance within gut microflora are avoided.[4]

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Accepted for publication 30 August 2001

Furthermore, some antimicrobials that can be used both systemically and topically may cause allergic sensitization of the skin or cross-resistance with systemic agents. Agents that are used only topically and have an efficacy at least equivalent to that of oral agents could be the most appropriate antimicrobials for the treatment of a range of skin infections. Mupirocin is a topical antimicrobial that rarely causes hypersensitivity reactions or other systemic effects, or shows cross-resistance with systemic antimicrobials.

The present study is the first comparing the efficacy and safety of a commonly used oral antimicrobial agent, cephalexin, with those of the topical agent, mupirocin calcium cream, in the treatment of secondarily infected eczema. This formulation has proven efficacy in the treatment of patients with secondarily infected wounds (small lacerations, abrasions or sutured wounds).[5] Furthermore, mupirocin itself has been shown to have antibacterial activity against the majority of aerobic Gram-positive cocci, including *Staphylococcus aureus*, *S. epidermis, Streptococcus pyogenes* and other β-haemolytic streptococci, which are common pathogens of skin infections.[6, 7]

Methods

Study design

Patients from 14 centres in the USA participated in this randomized, double-blind, double-dummy, parallel-group trial (Fig. 1). The study was approved by the investigational review board at each centre, and patients (or a parent or legal guardian) gave written informed consent.

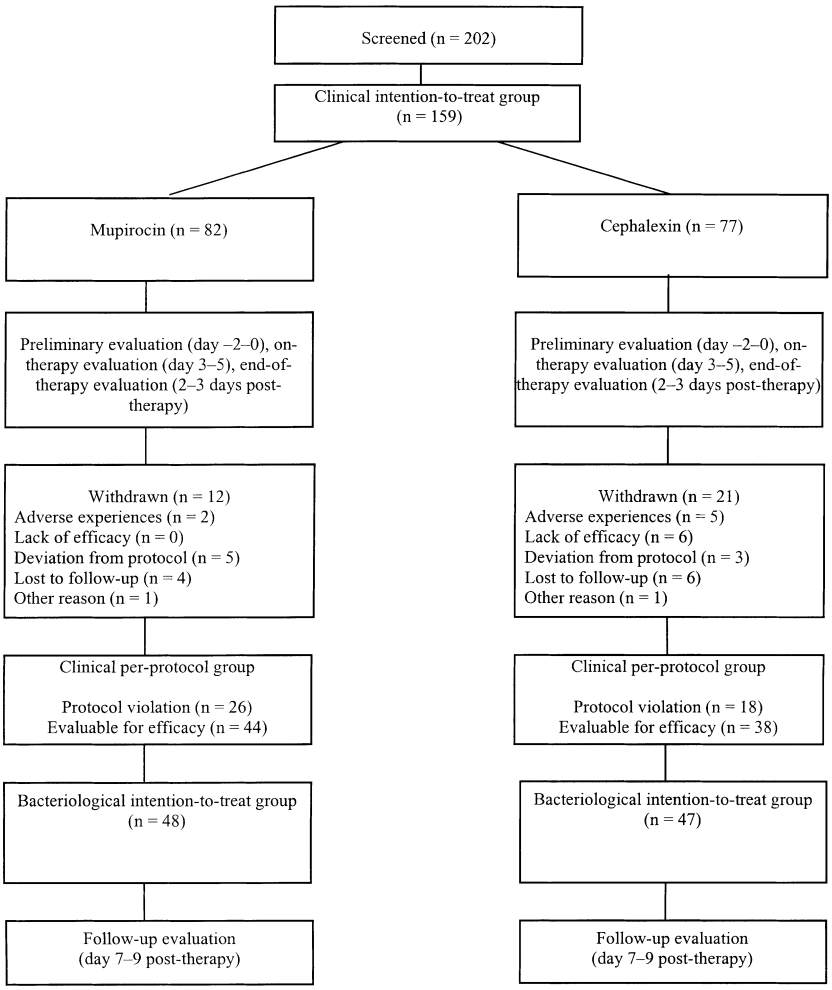

Figure 1 Study design.

Patients

Patients were eligible for entry into the trial if they were 8 years of age or older, weighed more than 40 kg, had secondarily infected eczema, and had a total skin infection rating scale (SIRS) score of at least 8 within the 48 h before starting study medication. The total SIRS score was calculated by adding together individual item scores for seven signs or symptoms: exudate/pus, crusting, erythema/inflammation, tissue warmth, tissue oedema, itching, and pain. The signs and symptoms were rated on a scale of 0–6, where 0 = absent, 2 = mild, 4 = moderate and 6 = severe.[8]

Patients were excluded from the study if they (i) had demonstrated a previous hypersensitivity reaction to penicillins, cephalosporins, other β-lactam antimicrobials or mupirocin; (ii) had a bacterial skin infection which, due to depth or severity, could not be appropriately treated with a topical antimicrobial; (iii) had received a systemic antibacterial or corticosteroid, or had applied any topical therapeutic agent (including corticosteroids) directly to the wound, or used soap containing an antibacterial agent within 24 h prior to entering the study; (iv) had a serious underlying disease; (v) were pregnant, breast-feeding or planning a pregnancy during the study; (vi) had used an investigational drug within 30 days prior to entering the study; or (vii) had been previously enrolled and subsequently excluded from this study.

Antimicrobial treatment

Patients were randomly assigned in a 1 : 1 ratio to treatment with topical 2% mupirocin calcium cream (Bactroban® Cream, Glaxo SmithKline) three times daily and oral placebo four times daily, or oral cephalexin (Keflex®, Dista Products) 250 mg four times daily and cream placebo three times daily, for 10 days. Treatment compliance was assessed using patient diary cards.

During the study, concomitant medications necessary for the health of the patient were permitted, except for systemic antimicrobials and corticosteroids, and topical therapies other than mupirocin applied to the infected area under investigation.

Evaluations

Assessments were made at baseline (within the 48 h before starting medication), 3–5 days after the start of treatment, and 2–3 days (end-of-therapy evaluations) and 7–9 days (follow-up) after the end of treatment. Patients' SIRS scores were determined and bacteriological specimens were obtained by twice swabbing a representative 4 × 4 cm area of the infected eczema. The first swab (taken with a Culturette® device) was cultured quantitatively for aerobic bacteria, while the second swab (taken using a Transwab® device) was cultured qualitatively for anaerobic bacteria.

The primary endpoint was clinical response at the end of therapy. The responses were classified as belonging to one of three categories, as defined in Table 1. The classifications of bacteriological responses are also shown in Table 1. Safety was assessed by interview at each visit. Adverse experiences were judged by the investigator to be 'not related', 'possibly related' or 'related' to the study drug. To assess patient preferences, patients were asked 'Do you prefer oral or topical therapy?' at the end-of-therapy visit.

Data analysis

The primary endpoint was clinical response in the per-protocol population at the end of therapy. Assuming a clinical response rate in the two groups of 93%, a

Table 1 Classifications of clinical and bacteriological responses used during the study

Clinical responses	
Success	Absence of exudate/pus, with or without complete resolution of other signs and symptoms of infection, a SIRS score of less than 8, and no use of additional antimicrobial
Failure	Presence of exudate/pus, a SIRS score of at least 8 and additional antimicrobial therapy administered
Unable to determine	A valid assessment of clinical outcome was not possible
Bacteriological responses	
Eradication	Pre-therapy pathogen eliminated
Improvement	Pre-therapy pathogen present but below 2% of the pre-therapy density
Colonization	Pre-therapy pathogen eradicated but an organism not present pre-therapy and not considered to be a pathogen isolated at the end of therapy
Superinfection	Pre-therapy pathogen eradicated but a different pathogen isolated at the end of therapy
Failure	Initial pathogen present at a density equal to or greater than the pre-therapy level
Unable to determine	A bacteriological evaluation could not be made

sample size of 150 evaluable patients per treatment was required to demonstrate with 90% power that the 95% confidence interval for a difference in clinical success rates between the two treatment groups was not greater than 10%.

Continuous data were analysed using the *t* test and categorical data using the χ^2 test. The difference in the success rates between treatment groups was analysed using a linear model with effects due to centre and treatment (Statistical Analysis System, version 6.07). A Wilcoxon rank sum test was performed to test for differences in the SIRS score between treatment groups. The equivalence of the two treatment groups was assessed by determining the two-tailed 95% confidence intervals of the difference in the proportions of patients with clinical and bacteriological successes. The treatment groups were considered equivalent if the 95% confidence limit of the difference in response was within ± 10%. Data were analysed for the population that completed the study according to protocol as well as the intent-to-treat population. (For the intent-to-treat analysis, patients whose outcome was 'unable to determine' were considered failures.)

Results

Patients

Due to enrolment that was slower than expected, only 159 patients were randomized to study medication (intent-to-treat group). Of these, 126 patients (79%) completed the study, and 82 patients (52%) were considered per-protocol evaluable for clinical efficacy at the end-of-therapy visit. The resulting power from this sample size was 85%. The demographic characteristics of the intent-to-treat population of patients are shown in Table 2.

Seventy-seven patients were excluded from the per-protocol evaluation of clinical efficacy at the end-of-therapy visit. The most common reasons for exclusion were a clinical assessment of 'unable to determine' (44 patients), failure to comply with the visit schedule (37 patients), less than 80% compliance with the study medication (22 patients), and too few or too many days on therapy (22 patients). Some patients were excluded for more than one reason.

Table 2 Demographic characteristics of patients in the intent-to-treat population

	Mupirocin cream ($n = 82$)	Cephalexin ($n = 77$)
Mean age, years ± SEM	41.5 ± 2.2	44.0 ± 2.3
(range)	(9–86)	(10–87)
Male/female	39/43	48/29
Race (*n*)		
White	56	57
Black	15	15
Oriental	5	2
Hispanic	5	3
Other	1	0

Of the patients completing the study, the most common sites for eczema were the face (26% of patients), the legs (15%), the palms (12%) and the dorsum of the feet (12%). For most patients, the area of skin affected by eczema was relatively small, consistent with localized disease.

Compliance with the antimicrobial regimen (greater than 80% and less than 120% of doses taken) was similar for the two groups (88% and 87% for the mupirocin cream and cephalexin groups, respectively).

Clinical responses

The mean SIRS scores at baseline for the clinical per-protocol population were 20.5 for the mupirocin group and 19.1 for the cephalexin group ($P = 0.09$). Clinical responses at the end-of-therapy visit were similar for the two treatment groups in both the per-protocol and intent-to-treat population (Table 3). At follow-up, the responses of 33 patients in the mupirocin group and

Table 3 Clinical responses at the end of therapy (per-protocol population)

	Number (%) of patients			
Response	Mupirocin cream	Cephalexin	95% confidence interval	*P* value
Per-protocol population				
Success	39/44 (89%)	31/38 (82%)	–8.4%, 22.5%	0.29
Failure	5/44 (11%)	7/38 (18%)		
Intent-to-treat population				
Success	52/82 (63%)	44/77 (57%)	–8.9%, 21.5%	0.38
Failure	30/82 (37%)	33/77 (43%)		

24 patients in the cephalexin group continued to be rated as clinical successes for the per-protocol population.

Bacteriological responses

Before therapy, 132 bacterial isolates (65 in the mupirocin group; 67 in the cephalexin group) were reported for 95 patients in the bacteriological intent-to-treat population (Table 4). Corresponding numbers for the bacteriological per-protocol population could not be obtained, as too few patients with pretreatment pathogens confirmed completed the protocol correctly. The primary endpoint of the study was clinical outcome. Hence, patients without a confirmed pathogen were considered evaluable for clinical outcome.

Of the 95 patients in the intent-to-treat population who had isolates cultured, 69 (73%) presented with one organism, 18 (19%) with two organisms, five (5%) with three organisms and three (3%) with four organisms. The pattern of organisms isolated was similar for the two treatment groups (Table 3). The most common isolate was *S. aureus* (56% of isolates) followed by *Acinetobacter lwoffi* (6% of isolates). *S. aureus* was isolated from 77% of patients in the mupirocin group and 79% of patients in the cephalexin group.

The bacteriological success rate was significantly higher in the mupirocin group than the cephalexin group (Table 5). This difference resulted primarily from the greater efficacy of mupirocin against *S. aureus* (Table 4). Eradication at the end of therapy was 70% for patients with *S. aureus* in the mupirocin group and 51% for cephalexin.

Table 4 Bacteria isolated from the intent-to-treat population

	Number of isolates		
	Mupirocin cream	Cephalexin	Total
Staphylococcus aureus			
Pre-therapy	37	37	74
End of therapy			
Eradicated or improved	26	19	45
Failed	0	6	6
Unable to determine	11	12	23
Follow-up			
Persistent eradication or improved	20	11	31
Relapse	4	7	11
Unable to determine	13	19	32
Acinetobacter lwoffi			
Pre-therapy	1	7	8
End of therapy			
Eradicated or improved	1	4	5
Failed	0	1	1
Unable to determine	0	2	2
Follow-up			
Persistent eradication or improved	0	2	2
Relapse	1	0	1
Unable to determine	0	5	5
Enterococcus species			
Pre-therapy	4	2	6
End of therapy			
Eradicated or improved	1	2	3
Failed	0	0	0
Unable to determine	3	0	3
Follow-up			
Persistent eradication or improved	1	1	2
Relapse	0	0	0
Unable to determine	3	1	4
Moraxella osloensis			
Pre-therapy	2	3	5
End of therapy			
Eradicated or improved	0	2	2
Failed	0	0	0
Unable to determine	2	1	3
Follow-up			
Persistent eradication or improved	0	1	1
Relapse	0	0	0
Unable to determine	2	2	4
Flavimonas oryzihabitans			
Pre-therapy	2	3	5
End of therapy			
Eradicated or improved	1	1	2
Failed	0	0	0
Unable to determine	1	2	3
Follow-up			
Persistent eradication or improved	1	0	1
Relapse	0	0	0
Unable to determine	1	3	4
Other bacteria	19	15	34

Adverse events

Seventeen of the 159 patients (11%) reported 25 adverse experiences related or possibly related to the study medication [7/82 patients in the mupirocin group (9%); 10/77 patients in the cephalexin group (13%); $P = 0.45$ between groups]. The most common adverse experiences overall were diarrhoea (2.4% of patients who received mupirocin; 3.9% who received cephalexin) and nausea (2.4% of patients who received mupirocin; 2.6% who received cephalexin). Application-site reactions (stinging and burning) were reported in 2.4% of patients receiving mupirocin and none who were receiving cephalexin.

Adverse experiences thought to be related or possibly related to study medication and considered to be severe in intensity were reported by three patients in the cephalexin group (one patient each with exacerbation of infection, exacerbation of eczema, and urticaria) and by no patients in the mupirocin group. Two patients in the mupirocin group and three in the cephalexin group were withdrawn because of adverse

Table 5 Bacteriological responses at the end of therapy (intent-to-treat population)

	Number (%) of patients		
Response	Mupirocin cream ($n = 48$)	Cephalexin ($n = 47$)	*P* value
Success	24 (50)	13 (28)	0.005
Eradication	23 (48)	8 (17)	(95% CI: 3.3%, 41.1%)
Improvement	1 (2)	5 (11)	
Failure	7 (15)	17 (36)	
Superinfection	6 (13)	10 (21)	
Failure	1 (2)	7 (15)	
Unable to determine	17 (35)	17 (36)	

experiences related or possibly related to the study medication. Adverse experiences that led to patient withdrawal were stinging and burning, with pruritus and dry skin at the application site in one patient receiving mupirocin, two patients with worsening eczema in the cephalexin group and one patient in each group with urticaria.

Patient acceptance

Of the 145 patients completing the end-of-treatment survey, 95 (65.5%) preferred topical therapy, 50 (34.4%) preferred oral therapy and 14 (9.7%) did not state a preference.

Discussion

This multicentre, double-blind, double-dummy, randomized study has demonstrated that topical antimicrobial treatment with mupirocin cream is at least as effective as systemic treatment with oral cephalexin for secondarily infected eczema of limited depth and severity. The clinical success rate (defined in part as a patient with a response of improvement in the SIRS) for the per-protocol population was 89% for mupirocin cream and 82% for cephalexin. No patient from the mupirocin group was withdrawn from the study because of a lack of therapeutic effect, whereas six patients from the cephalexin group were withdrawn for this reason.

Bacteriological success (defined as a patient with a response of eradication, improvement or colonization of bacteria at the end of therapy) was significantly higher in the mupirocin cream group (50% *vs* 28% for cephalexin) for the intent-to-treat population. The difference was attributed largely to the difference in efficacy against *S. aureus*, the most prevalent pre-therapy pathogen in each treatment group: bacteriological success rates for *S. aureus* were 70% in the mupirocin group and 51% in the cephalexin group.

Mupirocin has demonstrated activity against many multidrug-resistant staphylococci, including most that are methicillin-resistant.[6, 9] In one study, it was found to be active *in vitro* against 100% of 153 strains of *S. aureus* isolated from patients with infected eczema.[10] The ointment formulation (free acid in a polyethylene glycol base) has also been shown to dramatically reduce the mean number of *S. aureus* colony-forming units in the skin of patients with eczema.[6, 11]

The frequency of *S. aureus* isolation in this study (78% of patients and 56% of isolates) was less than that reported in previous studies of eczema.[1, 12, 13] The studies with the highest frequency of *S. aureus* isolation (> 90% of isolates) had younger patients and used the detergent scrub technique rather than the swab technique used in the present study.[1,13] Differences in isolates may also be the result of differences in the lesion sites.

In this study, the majority of patients indicated that the topical treatment was easy to apply, and almost twice as many patients expressed a preference for topical treatment compared with oral treatment.

Selection of the best antimicrobial regimen involves the consideration of multiple factors, in particular efficacy, the potential for adverse effects, the cost of treatment, and patient convenience. This study has shown that mupirocin is a viable alternative to systemic antimicrobial treatment because it is efficacious for secondarily infected eczema, well tolerated and frequently preferred by patients. In addition, this agent has excellent activity against *S. aureus,* which was the most common pre-therapy pathogen.

There have been reports of mupirocin resistance arising following therapy, and some investigators have expressed concern that expanded use of mupirocin may reduce its utility in the control of MSRA. However, the

majority of these reports of resistance are associated with long-term inappropriate usage in institutional settings. Current data suggest that short-term and intermittent treatment are unlikely to result in the development of clinically significant resistance, particularly in a community setting.[14]

Conclusions

Mupirocin cream applied three times daily is as effective clinically and superior bacteriologically compared with oral cephalexin given four times daily in the treatment of secondarily infected eczema of limited depth and severity. Mupirocin cream is as well tolerated as oral cephalexin, and more patients prefer the topical regimen, which should improve patient compliance.

Acknowledgements

This study was supported by a grant to each centre by Glaxo SmithKline Pharmaceuticals.

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