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Efficacy of a New Cream Formulation of Mupirocin: Comparison with Oral and Topical Agents in Experimental Skin Infections

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A new cream formulation of mupirocin developed to improve patient compliance was compared with systemic and topical antibiotics commonly used to treat primary and secondary skin infections. A mouse surgical wound model infected with *Staphylococcus aureus* or *Streptococcus pyogenes* was used. Topical treatment was applied at 4 and 10 h postinfection or oral treatment at a clinically relevant dose was administered 4, 8, and 12 h postinfection; treatments were continued three times daily for a further 3 days. Mupirocin cream was significantly more effective than ($P < 0.01$; two of eight studies) or not significantly different from (six of eight studies) mupirocin ointment in reducing bacterial numbers. Mupirocin cream was similar in efficacy to oral flucloxacillin but significantly more effective ($P < 0.001$) than oral erythromycin. It was also similar in efficacy to cephalexin against *S. pyogenes* but superior against *S. aureus* ($P < 0.01$). Mupirocin cream had a similar efficacy to fusidic acid cream against *S. aureus* but was significantly superior against *S. pyogenes* ($P < 0.01$). A hamster impetigo model infected with *S. aureus* was also used. Topical or oral treatment was administered at 24 and 30 h postinfection (also 36 h postinfection for oral therapy) and then three times daily for a further 2 days. On day 5, mupirocin cream was significantly more effective than mupirocin ointment in one study ($P < 0.01$) and of similar efficacy in the other two studies. Mupirocin cream was not significantly different from fusidic acid cream or neomycin-bacitracin cream, but it was significantly superior ($P < 0.01$) to oral erythromycin and cephalexin. Mupirocin cream was as effective as, or superior to, oral and other topical agents commonly used for skin infections.

Mupirocin (pseudomonic acid A) is the major metabolite produced by *Pseudomonas fluorescens* under submerged fermentation (19). Its mode of action, inhibition of isoleucyl-tRNA synthetase, is novel and differs from that of any available antibiotic. In vitro, mupirocin exhibits a high level of activity against gram-positive cocci such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, and other β-hemolytic streptococci (35), the pathogens most frequently encountered in primary and secondary skin infections. Initially formulated as 2% mupirocin ointment in a polyethylene glycol vehicle (Bactroban; SmithKline Beecham Pharmaceuticals), clinical usage over more than 10 years has demonstrated the efficacy and safety of mupirocin for treating primary and secondary skin infections (21, 25, 26, 28; A. A. Hebert, D. L. Breneman, and C. E. Grier, Prog. Abstr. 32nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1689, 1992). More recently, mupirocin as a 2% ointment in a soft white paraffin base has been shown to be highly effective in the elimination of nasal carriage of staphylococci, including methicillin-resistant *S. aureus* (9, 17, 18).

In general, topical ointment preparations are less acceptable to patients than cream formulations: creams are perceived to be easier to apply and to cause less garment soiling than ointments. To enhance patient acceptance and compliance, therefore, a new cream formulation of mupirocin has been developed.

In the studies reported here, a murine model of staphylococcal and streptococcal wound infections and a hamster model of staphylococcal impetigo were used to compare the efficacy of the new cream formulation of mupirocin with that of mupirocin ointment and their respective vehicle placebos and of systemically or topically administered antibiotics commonly used in the treatment of skin infections.

MATERIALS AND METHODS

Experimental animals. Female MF1 mice, weighing 18 to 22 g, were obtained from Harlan OLAC, Bicester, United Kingdom, and housed in polycarbonate cages containing five animals each. Male golden Syrian hamsters, 80 to 100 g, were obtained from Wrights, Essex, United Kingdom, and housed individually. All animals were given food and water ad libitum. Animal experimentation was regulated by the Animals (Scientific Procedures) Act 1986, and procedures were examined by an internal review board.

Organisms. All organisms were isolates from skin infections. Table 1 shows their susceptibility to mupirocin and a range of commonly used antibiotics. Staphylococci were stored on nutrient agar slants, and broth cultures were grown at 37°C in veal infusion broth (Difco Laboratories, East Molesey, United Kingdom). Broth cultures of the streptococci were grown in Todd-Hewitt broth (Oxoid, Basingstoke, United Kingdom) seeded from aliquots stored at −80°C.

Antibiotics. All materials were supplied by SmithKline Beecham Pharmaceuticals, Bristol, Tenn. Mupirocin was supplied either as a 2% ointment formulation in a polyethylene glycol base (Bactroban) or as a 2% cream formulation in an oil-water emulsion base. Each vehicle, devoid of the active ingredient, served as a placebo. Fusidic acid cream and neomycin-bacitracin cream were commercial preparations (Fucidin; Leo Laboratories, Princes Risborough, United Kingdom; Cicatrin; The Wellcome Foundation, London, United Kingdom). All topical agents were dispensed into sterile 1-ml syringes prior to use and stored at 4°C. Erythromycin base was supplied by the Upjohn Co., Ltd., Crawley, United Kingdom. The powder was dissolved in 100% ethanol at 50 times the required concentration and then diluted in sterile distilled water. Flucloxacillin sodium salt (SmithKline Beecham Pharmaceuticals, Worthing, United Kingdom) was dissolved in sterile distilled water. Cephalexin (Keflex; Eli Lilly & Co., Basingstoke, United Kingdom) capsules were emptied, and the contents were mixed

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TABLE 1. In vitro susceptibility of the infecting organisms to mupirocin and a range of commonly used antibiotics

Organism	MIC of test agents (μg/ml)								
	Mupirocin	Erythromycin	Flucloxacillin	Cephalexin	Fusidic acid	Neomycin	Bacitracin	Benzylpenicillin	Methicillin
S. aureus Sweeting	0.12	>128	0.12		0.25			0.03	1.0
S. aureus J1225	0.12	0.12	0.25	2.0	0.03	16	1.0	32	2.0
S. pyogenes 1580	0.25	0.06	0.06		8.0			≤0.007	0.25
S. pyogenes PA52	0.25	0.06	0.06	1.0	8.0	>16	1.0	≤0.007	0.25

with equal parts of gum acacia and made into suspensions with sterile distilled water to the required concentration. Fresh antibiotic solutions were prepared on a daily basis and stored at 4°C.

Mouse wound infection model. Sterile silk sutures (Mersilk, Ethicon, Ltd.) were cut into 10-cm lengths and soaked in undiluted overnight broth cultures of the organisms (10^8 CFU/ml) for 30 min. The sutures were removed aseptically, dried on sterile filter paper, and then threaded onto sterile surgical needles and stored at 4°C until the animals were prepared for surgery. To enumerate the organisms carried on the sutures, 1-cm lengths ($n = 3$) were vortexed for 10 min in 1 ml of 0.2% yeast extract (Oxoid) for the staphylococci or in Todd-Hewitt broth for the streptococci. The resulting suspensions were serially diluted, and 20-μl volumes of each dilution were plated in triplicate onto CLED agar (Oxoid), which was incubated for 24 h, to enumerate *S. aureus. S. pyogenes* suspensions were cultured on 5% horse blood agar (Oxoid) and incubated for 48 h. The numbers of organisms per centimeter of suture were calculated. Anesthesia was induced by intramuscular injection of diazepam (Valium; Roche Products, Ltd., Welwyn Garden City, United Kingdom) at 1.25 mg/kg, along with fentanyl fluanisone (Hypnorm; Janssen, Saunderton, United Kingdom) at 0.5 ml/kg. The fur on the back and flanks was clipped, and the skin swabbed with 70% ethanol. By using the threaded needle, a 1-cm length of inoculated suture was inserted under the skin of the mid-back and secured by knotting. An incision was made along the length of the suture down to, but not into, the panniculus carnosus. One wound was created per animal. The wound was closed with an adhesive temporary skin closure (Steristrip; 3M, Minneapolis, Minn.), and the animals were allowed to recover.

Treatment was initiated at 4 h after surgery. Development studies showed that at this time the bacterial counts in the wounds varied from the starting inoculum by no more than 0.5 $\log_{10}$. Mupirocin ointment, mupirocin cream, their respective vehicle placebos, or fusidic acid cream was applied in a 0.1-ml volume to the wound and was spread over the area. A second application was made 6 h later, and therapy was continued three times daily for a further 3 days. Erythromycin (200 mg/kg), cephalexin (20 mg/kg), and flucloxacillin (100 mg/kg) were given orally by gavage in 0.2 ml. These doses were chosen because, in preliminary experiments, they were found to produce peak serum levels in the mouse of the same order as those reported in humans (Table 2) (23, 27, 36). After an initial dose at 4 h, oral treatment continued at 8 and 12 h postinfection and then three times daily for a further 3 days.

All topical and systemic treatments were given to groups of 10 animals, and a further group was left untreated to serve as infection controls. On day 5 after surgery, 16 to 20 h after the last topical application or oral dose, the animals were humanely killed by CO_2 asphyxiation. Fur around the wound site was reclipped if necessary, and the area lightly swabbed with 70% ethanol. A 1-by-2-cm area of skin, including the wound, was excised and homogenized in 1 ml of either 0.2% yeast extract or Todd-Hewitt broth in glass tissue grinders. The homogenates were serially diluted, and the organisms were enumerated as previously described. Bacterial counts were expressed as means ± standard deviations.

The optimal methods for prevention of antibiotic carryover during the in vitro procedures were determined in pilot experiments with a charcoal-supplemented medium. Charcoal is reported to bind mupirocin non-specifically, permitting the growth of staphylococci and increasing the sensitivity of detection by 10,000-fold (3). Published methods used mupirocin ointment (3); subsequent studies done in house (data not reported) showed that the charcoal method gave similar results when the source of mupirocin was the cream formulation or a laboratory reference powder. In pilot experiments on mouse skin wounds, concentrations of residual mupirocin in the homogenates 20 h after exposure to mupirocin topical treatment were typically between 5 and 98 μg/ml for the ointment and between 85 and 750 μg/ml for the cream. Inocula containing 10^2, 10^4, or 10^6 CFU of the test strains were exposed in vitro to mupirocin at 1,000 μg/ml in broth; spread onto 5% horse blood agar supplemented with 0.5, 1, 2, 3, or 4% activated charcoal (Sigma Chemical Co., Ltd., Poole, United Kingdom); and incubated for 24 or 48 h. For *S. aureus*, a minimum period of incubation of 48 h on agar containing 2% charcoal gave the optimum results in terms of elimination of carryover and visualization of colonies from small inocula. The strains of *S. pyogenes* failed to grow on charcoal blood agar in the absence of mupirocin. In this case, the use of porcine liver esterase (Sigma) was investigated (40). The addition of 250 U of the esterase per 200 μl of streptococcal culture was found to be satisfactory for the removal of mupirocin prior to inoculation of blood agar.

Hamster impetigo model. Animals were anesthetized by inhalation of isoflurane (Abbott Laboratories, Queenborough, United Kingdom), 3% in O_2-NO_2 for induction, reduced to a maintenance dose of 1.5%. The back and flanks were clipped and swabbed, and a grid defining four quadrants of approximately 4 by 3 cm was drawn on the back. Into each quadrant, 100 μl of a log-phase culture of *S. aureus* J1225 was inoculated intradermally. Injection sites were thus approximately 3 cm apart.

Treatment commenced 24 h after infection, by which time lesions had formed and the bacterial counts per lesion were within 0.5 $\log_{10}$ of the starting inoculum. Treatment comprised 0.05 ml of one of the topical treatments (mupirocin cream, mupirocin ointment, one of the two vehicle placebos, fusidic acid cream, or neomycin-bacitracin cream) or one of the oral treatments (oral erythromycin at a dose of 100 mg/kg or oral cephalexin at a dose of 40 mg/kg). The doses of erythromycin and cephalexin were chosen after preliminary experiments to assess the comparability of peak serum levels in the hamster with those attained in humans (Table 2). The four lesions on each animal received the same topical treatment. A second dose was administered 6 h later, in the case of topical treatments, and 6 and 12 h later in the case of oral treatments. All treatments were continued three times daily for a further 2 days. Each treatment was given to groups of four hamsters; thus, 16 lesions were treated. One group of four hamsters was left untreated as controls. The size and appearance of the lesions were recorded at the start and end of therapy. On day 5 of the study, 20 h after cessation of therapy, the animals were humanely killed by pentobarbitone overdose. Each lesion and surrounding skin (approximately 5 mm^2) was excised and homogenized to enumerate staphylococci as described above, using the activated charcoal method to negate antibiotic carryover.

Statistical analysis. In each model, the following comparisons were made: placebo treatment versus no treatment; each mupirocin treatment versus its respective vehicle placebo; mupirocin cream versus mupirocin ointment; mupirocin cream (or ointment) versus comparator (oral or topical); and comparator (oral or topical) versus no treatment. Each comparison was made using the

TABLE 2. Comparison of peak serum concentrations of the systemic agents used in the mouse and the hamster with those attainable in humans after oral administration

Agent	Mouse		Hamster		Human	
	Dose (mg/kg)	Peak serum concn ± SD (μg/ml [range])	Dose (mg/kg)	Peak serum concn ± SD (μg/ml [range])	Dose (mg)	Peak serum concn ± SD (μg/ml [range])
Erythromycin	200	3.8 ± 2.1 [1.7–7.8]	200[a]	12.1 ± 5.1 [6.2–15.2]	250[c]	0.93 ± 0.23
Flucloxacillin	100	18.0 ± 13.0 [4.5–39.5]			500[d]	14.5 [3.4–26.5]
Cephalexin	20	15.4 ± 2.3 [12.6–18.8]	20[b]	3.7 ± 0.6 [3.2–4.5]	250[e]	7.3 ± 2.5 [3.6–11.0]

[a] Dose used in efficacy tests was 100 mg/kg.
[b] Dose used in efficacy tests was 40 mg/kg.
[c] Reference 27.
[d] Reference 36.
[e] Reference 23.

TABLE 3. Mean bacterial counts from surgical wound infections in the mouse following treatment with mupirocin cream, mupirocin ointment and their respective placebos

Treatment	Mean bacterial count (log_{10} CFU/wound) ± SD (no. of wounds)[d]			
	S. aureus		*S. pyogenes*	
	Sweeting	J1225	1580	PA52
Implantation	~5.0	4.64 ± 0.2	4.26 ± 0.20	3.96 ± 0.21
After 5 days				
Untreated	7.23 ± 0.33 (10)	7.46 ± 0.63 (10)	6.14 ± 1.11 (9)	7.10 ± 0.60 (10)
Placebo cream	7.52 ± 0.40 (10)	7.45 ± 0.38 (10)	6.52 ± 1.33 (9)	6.85 ± 0.60 (10)
Placebo ointment	7.16 ± 0.43 (10)	7.21 ± 0.24 (10)	6.32 ± 1.40 (8)	6.56 ± 0.45 (9)
Mupirocin cream	2.51 ± 1.69[a,b] (10)	1.55 ± 0.58[a] (10)	1.34 ± 0.80[a,c] (10)	1.90 ± 1.68[a] (9)
Mupirocin ointment	4.62 ± 2.15[a] (8)	2.54 ± 2.24[a] (10)	3.92 ± 1.11[a] (8)	2.56 ± 1.92[a] (9)

[a] $P < 0.001$ versus respective vehicle placebo and untreated controls.
[b] $P = 0.01$ versus mupirocin ointment.
[c] $P < 0.01$ versus mupirocin ointment.
[d] Animals that had removed sutures during the treatment period were excluded from the analyses.

Student's *t* test with Bonferroni's correction for multiple comparisons and, in each test, the null hypothesis was that there was no significant difference between treatments. *P* values of ≤0.01 were considered significant. Mice that had removed sutures during the treatment period were excluded from the analyses, as such infections resolve quickly in the absence of active treatment (unpublished observations). Likewise, sites in the impetigo model that did not produce lesions were also excluded.

RESULTS

Staphylococcal mouse wound infections. (i) Comparison of mupirocin cream with mupirocin ointment and their respective vehicle placebos. At day 5, the mean bacterial counts for wounds treated with mupirocin formulations were significantly lower than those for their respective vehicle placebos ($P < 0.001$), and there were no significant differences between placebos and untreated controls (Table 3). Mupirocin cream had eradicated *S. aureus* Sweeting from 4 of the 10 treated wounds (<10 CFU) and reduced the mean count to 2.51 ± 1.69 log_{10} CFU/wound. Therapy with mupirocin ointment reduced the mean count to 4.62 ± 2.15 log_{10}/wound; of the eight evaluable wounds, three (38%) had bacterial counts of 2.50 log_{10} CFU/wound or less, while the five remaining wounds contained 5 to 6 log_{10} CFU/wound.

In the case of *S. aureus* J1225, mupirocin cream-treated wounds had a mean count of 1.55 ± 0.58 log_{10} CFU/wound; 4 of the 10 wounds had no staphylococci, while the remaining 6 wounds contained 2.55 log_{10} CFU/wound or less. Therapy with mupirocin ointment reduced the mean count to 2.54 ± 2.24 log_{10} CFU/wound.

Mupirocin cream was significantly superior to mupirocin ointment in reducing the numbers of *S. aureus* Sweeting in infected wounds ($P = 0.01$), but the two treatments were not significantly different for the J1225 strain infection ($P = 0.42$).

(ii) Comparison of mupirocin cream with mupirocin ointment, oral erythromycin, and flucloxacillin. The mean bacterial count for wounds infected with *S. aureus* J1225 and treated with mupirocin cream was significantly lower than that for oral erythromycin ($P < 0.001$), but it was not significantly different from those for wounds treated with mupirocin ointment ($P = 0.038$) or flucloxacillin ($P = 0.24$) (trial 1 [Table 4]). All active treatments significantly reduced the mean bacterial counts compared with untreated controls ($P < 0.001$ in all cases).

(iii) Comparison of mupirocin cream with mupirocin ointment, oral cephalexin, and topical fusidic acid. The mean count for infections with *S. aureus* J1225 treated with mupiro-

TABLE 4. Mean bacterial counts from surgical wound infections in the mouse after treatment with mupirocin cream, mupirocin ointment, and oral and other topical agents commonly used to treat skin infections

Treatment	Mean bacterial count (log_{10} CFU/wound) ± SD (no. of wounds)[e]			
	S. aureus J1225		*S. pyogenes* PA52	
	Trial 1	Trial 2	Trial 1	Trial 2
Implantation	4.60 ± 0.13	4.70 ± 0.14	4.19 ± 0.19	4.38 ± 0.41
After 5 days				
Untreated	7.27 ± 0.23 (10)	7.42 ± 0.24 (10)	6.69 ± 1.54 (9)	7.77 ± 0.51 (10)
Mupirocin cream	1.89 ± 1.57[a,b] (9)	1.45 ± 1.05[a,c] (8)	1.00[a,b] (10)	1.76 ± 1.11[a,d] (9)
Mupirocin ointment	3.49 ± 1.90[a] (8)	3.39 ± 2.11[a,c] (9)	1.47 ± 0.66[a,b] (9)	2.80 ± 1.85[a] (8)
Erythromycin, 200 mg/kg (p.o.)	3.11 ± 0.98[a] (10)		3.78 ± 1.27[a] (10)	
Flucloxacillin, 100 mg/kg (p.o.)	2.89 ± 1.96[a] (10)		1.28 ± 0.65[a,b] (9)	
Cephalexin, 20 mg/kg (p.o.)		5.86 ± 0.51[a] (8)		3.52 ± 1.90[a] (10)
Fusidic acid cream		2.47 ± 2.11[a,c] (8)		6.51 ± 0.72[a] (6)

[a] $P < 0.001$ versus untreated controls.
[b] $P < 0.001$ versus erythromycin.
[c] $P < 0.01$ versus cephalexin.
[d] $P < 0.01$ versus fusidic acid.
[e] Animals that had removed sutures during the treatment period were excluded from the analyses. p.o., peroral.

TABLE 5. Mean bacterial counts from impetigo lesions in the hamster caused by *S. aureus* J1225 after treatment with mupirocin cream, mupirocin ointment, and oral and other topical agents commonly used to treat skin infections

Treatment	Mean bacterial count ($\log_{10}$ CFU/lesion) ± SD (no. of lesions)[e]		
	Trial 1	Trial 2	Trial 3
Inoculation	7.46	6.93	7.13
After 5 days			
Untreated	5.92 ± 0.73 (15)	6.20 ± 1.28 (16)	5.32 ± 1.25 (16)
Placebo cream	4.46 ± 1.24[a] (16)		
Placebo ointment	4.56 ± 1.16[a] (14)		
Mupirocin cream	2.29 ± 0.87[b,c] (14)	2.23 ± 1.38[a,d] (16)	2.75 ± 1.11[a] (16)
Mupirocin ointment	3.32 ± 1.02[b] (15)	3.11 ± 1.06[a,d] (16)	2.93 ± 0.90[a] (16)
Erythromycin, 100 mg/kg (p.o.)		4.60 ± 0.93[a] (16)	
Cephalexin, 40 mg/kg (p.o.)		4.66 ± 0.86[a] (16)	
Fusidic acid cream			2.54 ± 1.09[a] (15)
Neomycin-bacitracin cream			3.15 ± 1.05[a] (16)

[a] $P < 0.01$ versus nontreated controls.
[b] $P < 0.01$ versus placebo.
[c] $P < 0.01$ versus mupirocin ointment.
[d] $P < 0.01$ versus erythromycin and cephalexin.
[e] Inoculated sites that did not produce lesions were excluded from the analyses. p.o., peroral.

cin cream was 1.45 ± 1.05 $\log_{10}$ CFU/wound, with six of the eight evaluable wounds being sterile (<10 CFU), while the mean count for mice treated with mupirocin ointment was 3.39 ± 2.11 $\log_{10}$ CFU/wound, with three of the nine evaluable wounds being sterile (trial 2 [Table 4]). Therapy with fusidic acid cream reduced the mean count to 2.47 ± 2.11 $\log_{10}$ CFU/wound and sterilized four of the eight wounds, whereas oral cephalexin treatment failed to eliminate staphylococci from any of the wounds (mean count, 5.86 ± 0.51 $\log_{10}$ CFU/wound). In this infection, the effect of mupirocin cream was not significantly different from that of mupirocin ointment or fusidic acid cream ($P > 0.01$); all topical treatments were significantly more effective than oral cephalexin ($P < 0.01$ in each case). All active treatments significantly reduced the mean bacterial counts compared with untreated controls ($P < 0.001$ in all cases).

Streptococcal mouse wound infection. (i) Comparison of mupirocin cream with mupirocin ointment and their respective vehicle placebos. At day 5, the mean bacterial counts for wounds treated with mupirocin formulations were significantly lower than those for their respective vehicle placebos ($P < 0.001$ in each case), and there were no significant differences between placebos and untreated controls (Table 3). Mupirocin cream eradicated *S. pyogenes* 1580 from 8 of the 10 wounds and gave a mean count of 1.34 ± 0.80 $\log_{10}$ CFU/wound (Table 3). In contrast, mupirocin ointment reduced the mean count to 3.92 ± 1.11 $\log_{10}$ CFU/wound in eight evaluable wounds, the sutures having been removed by the remaining two animals. Mupirocin cream was significantly more efficacious than mupirocin ointment ($P < 0.01$).

Mupirocin cream and mupirocin ointment reduced the mean bacterial counts for *S. pyogenes* PA52 to 1.90 ± 1.68 and 2.56 ± 1.92 $\log_{10}$ CFU/wound, respectively, by day 5. One animal in each treatment group was excluded from the analysis due to removal of the suture. In this infection, the efficacies of the active treatments were not significantly different ($P = 0.25$).

(ii) Comparison of mupirocin cream with mupirocin ointment, oral erythromycin, and flucloxacillin. All wounds treated with mupirocin cream were devoid (<10 CFU/wound) of the infecting organism, *S. pyogenes* PA52, as were five of the nine evaluable wounds treated with mupirocin ointment (mean count, 1.47 ± 0.66 $\log_{10}$ CFU/wound; trial 1 [Table 4]). The efficacies of the mupirocin formulations and flucloxacillin were similar, but all were significantly more effective than erythromycin ($P < 0.001$ in each case). All active treatments significantly reduced the mean bacterial counts compared with untreated controls ($P < 0.001$ in all cases).

(iii) Comparison of mupirocin cream with mupirocin ointment, oral cephalexin, and topical fusidic acid. Six of the nine evaluable wounds infected with *S. pyogenes* PA52 and treated with mupirocin cream had bacterial counts close to or below the limit of detection (10 CFU/wound), and the mean count was 1.76 ± 1.11 $\log_{10}$ CFU/wound (trial 2 [Table 4]). Comparison of the treatment groups showed no difference between mupirocin cream and mupirocin ointment ($P = 0.09$) or oral cephalexin ($P > 0.01$), but mupirocin cream was significantly more effective than fusidic acid cream ($P < 0.01$). All active treatments significantly reduced the mean bacterial counts compared with untreated controls ($P < 0.001$ in all cases).

Hamster staphylococcal impetigo. (i) Comparison of mupirocin cream with mupirocin ointment and their respective vehicle placebos. After inoculation with *S. aureus* J1225, lesions developed at 74 (93%) of the 80 injected sites. By 24 h after inoculation, lesions were pustular or vesicular in appearance, were 1 to 6 mm in diameter, and had an erythematous rim. The majority of lesions became crusted by 48 h after infection. Of 16 lesions in the group of untreated animals, 1 (6.3%) had re-epithelialized and was assessed as healed, while the remaining lesions were crusted. In the mupirocin-treated animals 24.1% (7 of 29 lesions) were assessed as healed compared with 9.4% (3 of 32 lesions) in placebo-treated animals. In this study, mupirocin cream was more effective than mupirocin ointment ($P < 0.01$) (trial 1 [Table 5]). Placebo treatments had a significant effect on mean bacterial counts compared with untreated animals ($P < 0.01$ in each case), and the mean bacterial counts for wounds treated with mupirocin formulations were significantly lower than those for their respective vehicle placebos ($P < 0.01$ in each case).

(ii) Comparison of mupirocin cream with mupirocin ointment, oral erythromycin, and cephalexin. Treatment with mupirocin cream or ointment was significantly more efficacious than with erythromycin or cephalexin ($P < 0.01$) (trial 2 [Table 5]). Mean bacterial counts from lesions after all active treat-

ments were lower than in the untreated controls ($P < 0.01$ in each case).

(iii) Comparison of mupirocin cream with mupirocin ointment, fusidic acid, and neomycin-bacitracin. Vesicular or pustular lesions had developed in 111 (99%) of the 112 sites 24 h after inoculation with *S. aureus* J1225. In this study, the efficacy of mupirocin cream was not significantly different from that of mupirocin ointment ($P = 0.31$), fusidic acid ($P = 0.36$), or neomycin-bacitracin ($P = 0.15$) (trial 3 [Table 5]). Mean bacterial counts from lesions after active treatment were lower than in the untreated controls ($P < 0.01$ in each case).

DISCUSSION

Impetigo is the most common primary skin infection; it is highly contagious and occurs mainly in children. While changes in the etiology of impetigo have been reported, with approximately one-half of infections now being caused by *S. aureus*, group A streptococci remain important pathogens in over a third of cases of impetigo (4) and in infections such as erysipelas and cellulitis. Impetigo lesions in the hamster bear clinical and histological similarities to those seen in humans (12, 15), and the model has been used to assess various therapeutic regimens (14).

The murine model of skin wound infection is established by implanting contaminated sutures (29) and represents the secondary skin infections that may occur following damage by accidental trauma, surgery, and burns or as a result of superinfection of an underlying skin disease. Such foreign-body infections are a stringent test of the efficacy of antibiotics.

The discriminative models utilized in the studies reported here have been used previously for evaluating systemic and topical antimicrobial agents (5, 6, 14, 29), and the data have been shown to correlate well with efficacy in humans. The results reported here show that the new cream formulation of mupirocin was as effective as the established ointment preparation and, in two of eight trials, it was more efficacious for treating staphylococcal and streptococcal infections. Mupirocin cream was also superior to oral erythromycin and, for the most part, to cephalexin. While the systemic agents resulted in marked reductions in staphylococcal and streptococcal counts at clinically relevant doses, therapy with mupirocin cream was more effective and resulted in more wounds or lesions being sterilized. These results reflect clinical findings of the last 10 years for the use of erythromycin and mupirocin ointment in treating impetigo. Response rates to mupirocin have been between 80 and 98%, while a more variable response to erythromycin of 44 to 96% has been reported (1). Cephalexin has been shown to be as effective clinically as erythromycin in treating impetigo (16), but neither systemic agent was as efficacious as mupirocin cream in the treatment of an experimental staphylococcal impetigo.

The efficacy of mupirocin cream in the mouse model did not differ significantly from that of flucloxacillin, correlating well with results of clinical studies comparing mupirocin ointment with the oral isoxazolyl penicillin (38). Similarly, the efficacy of mupirocin cream was not significantly different from that of neomycin-bacitracin in the treatment of experimental impetigo. In clinical studies, however, topical preparations of neomycin-bacitracin-polymyxin B or neomycin-polymyxin B have been shown to be less effective than mupirocin ointment (26, 43).

There was no difference in the efficacies of mupirocin cream and topical fusidic acid for treating experimental infections caused by *S. aureus*, supporting clinical findings (20, 25, 30, 41). Fusidic acid is, however, less active against streptococci and was significantly less effective than mupirocin cream for treating wounds infected with *S. pyogenes*.

Erythromycin, flucloxacillin, and cephalexin are preferred by many clinicians for treating superficial skin infections. The use of erythromycin in some geographical areas may be restricted, however, due to the high incidence of erythromycin-resistant *S. aureus* and rapidly increasing incidence of macrolide-resistant *S. pyogenes* in the etiology of impetigo (13, 33). Additional factors limiting the use of erythromycin and other oral agents are gastrointestinal side effects (32; Hebert et al., 32nd ICAAC) and the frequency of administration, both of which may lead to reduced compliance. Adherence to treatment was lower in patients receiving oral erythromycin four times daily compared with those using topical mupirocin ointment three times daily (8), supporting the principle that patients are more compliant when given simple and less-frequent dosing regimens (10). Topical agents may also be more attractive than oral therapy because they reduce the potential for systemic side effects, such as nausea and diarrhea, and avoid resistance selection in the gut flora. In addition, application of the antibiotic directly to the infected lesion also results in higher local concentrations at the site of action and consequently allows overall use of the drug to be reduced.

The ideal topical antibiotic should have a sufficiently broad spectrum of activity to be used as a single agent, must not promote cross-resistance or multiple resistance, and should be unrelated to systemically administered agents. It should also be well tolerated with a low potential for side effects. While many topical antibiotics currently available do possess some of these attributes, topical mupirocin is closer to the ideal.

Mupirocin has excellent activity against the major skin pathogens while having little effect on commensals that contribute to the natural defenses of the skin (35; J. E. Finlay, L. A. Miller, and J. A. Poupard, Proc. 19th Int. Cong. Chemother., abstr. 4164, 1995). The unique mode of action of mupirocin, inhibition of isoleucyl-tRNA synthetase (22), is thought to be a major contributory factor to its lack of cross-resistance to other antibiotics (42). While cross-resistance with fusidic acid is also rare, fusidic acid-resistant bacteria are frequently resistant to penicillin and sometimes to tetracycline or erythromycin (34). These antibiotics may therefore exert a selective pressure on the general level of fusidic acid resistance, and circumstantial evidence of this has been reported (2, 31). Development of resistance to topical fusidic acid and neomycin is, however, potentially serious as the efficacy of systemically administered preparations could be compromised.

Reports of the isolation of mupirocin-resistant *S. aureus* remain sporadic despite its relatively widespread use. A 1990 survey found that 99.7% of isolates of *S. aureus* ($n = 7,137$) were susceptible to mupirocin compared to 97.3% to fusidic acid (11).

Topical antibiotics generally have different and fewer side effects compared with systemic agents. Use of mupirocin ointment for over a decade has shown that it is extremely well tolerated and that side effects, such as itching, burning, rash, or dry skin, are minor (7, 39; Hebert et al., 32nd ICAAC). Mupirocin also lacks the potential to cause photosensitive irritant reactions and contact sensitization (25, 37), the latter being associated with the use of topical chloramphenicol and neomycin sulfate.

While the safety profiles of topical antibiotics are generally good, patient acceptance of ointments is, in general, lower than that of cream preparations. Ointments have higher viscosities than cream formulations, leading to difficulties in application to skin lesions, and patients may report garment soiling from greasy residues. Such observations drove the development of

the cream formulation of mupirocin, which is anticipated to enhance patient acceptance and compliance.

Overall, the experimental data show that the efficacy of mupirocin cream compares favorably with those of currently used topical and oral agents. On the grounds of efficacy and improved patient compliance compared with mupirocin ointment and systemic therapies, mupirocin cream should therefore have a significant role in the treatment of primary and secondary skin infections.

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