IN-VITRO COMPARISON TO EVALUATE THE EFFECT OF DIFFERENT VEHICLES IN THE EFFECTIVENESS OF TOPICALLY APPLIED MUPIROCIN

BY

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ABSTRACT

The efficacy of a new topical antiinfective agent, mupirocin in different vehicles, was compared with that of oral erythromycin. The relative activity of Mupirocin in topically applied formulations using different vehicles (ointment and cream) versus oral erythromycin was evaluated by antimicrobial activity studies. Vehicles can play a great role in enhancing drug release and imparting superior antimicrobial activity when the drug was entirely solubilized. Furthermore, drug release and in vivo response demonstrated the usefulness of in vitro release studies in predicting vehicle efficacy. The evaluation of ointment and Mupirocin cream vehicles with oral erythromycin were studied in experimental skin infections.

A mouse surgical wound model infected with \textit{Staphylococcus aureus} or \textit{Streptococcus pyogenes} was used. Topical Mupirocin treatment was applied at 4 and 10 h postinfection oral erythromycin 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 (\textit{P < 0.01}; two of eight studies) Mupirocin ointment in reducing bacterial numbers. Mupirocin cream was similar in efficacy to oral erythromycin. Mupirocin cream had efficacy against \textit{S. aureus} but was significantly superior against \textit{S. pyogenes} (\textit{P < 0.01}). A hamster impetigo model infected with \textit{S. aureus} was also used. Topical Mupirocin or oral erythromycin 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 the study (\textit{P < 0.01}). In impetigo infection Mupirocin cream was significantly superior (\textit{P < 0.01}) to oral erythromycin against \textit{S. aureus}. 

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KEY WORDS: Topical Mupirocin, vehicles, oral erythromycin, experimental skin infections.

INTRODUCTION

Mupirocin (pseudomonic acid A) is the major metabolite produced by *Pseudomonas fluorescens* under submerged fermentation\(^\text{19}\). 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\(^\text{35}\), the pathogens most frequently encountered in primary and secondary skin infections.
infections. Initially formulated as 2% Mupirocin ointment in a polyethylene glycol vehicle (Julphar Pharmaceuticals, Ras Alkeimah, UAE), clinical usage over more than 10 years has demonstrated the efficacy and safety of Mupirocin for treating primary and secondary skin infections \(^{21,25,26,28}\). More recently, Mupirocin as a 2% ointment in a soft white paraffin base (Boots Pharmacy, Dubai, UAE) has been shown to be highly effective against *staphylococci* and 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 evaluate the antimicrobial effect of the drug in different vehicles therefore, a comparison between Mupirocin in cream and ointment bases was investigated.

In the studies reported here, a simulated model of staphylococcal and streptococcal wound infections and a hamster model of staphylococcal impetigo were used to compare the efficacy of Mupirocin formulations in different vehicles and their respective vehicle placebos and of systemically erythromycin.

**MATERIALS AND METHODS**

**Experimental animals:** Female MF1 mice, weighing 18 to 22 g, were obtained from Pharmacology department, Dubai Medical College, housed in polycarbonate cages containing five animals each. Male golden Syrian hamsters, 80 to 100 g, were obtained from Dubai research Center, 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 (Julphar Pharmaceuticals, Ras Alkeimah, UAE). Broth cultures of the streptococci were grown in Todd-Hewitt broth (Julphar Pharmaceuticals, Ras Alkeimah, UAE) seeded from aliquots stored at −80°C.
Antibiotics. All materials were supplied by Julphar Pharmaceuticals, Ras Alkeimah, UAE. Mupirocin was prepared as a 2% ointment formulation in a polyethylene glycol base and as a 2% cream formulation in an oil-water emulsion base. Each vehicle, devoid of the active ingredient, served as a placebo. All topical agents were dispensed into sterile 1-ml syringes prior to use and stored at 4°C. Erythromycin powder (Julphar Pharmaceuticals, Ras Alkeimah, UAE) was dissolved in 100% ethanol at 50 times the required concentration and then diluted in sterile distilled water. Fresh antibiotic solutions were prepared on a daily basis and stored at 4°C.

Mouse wound infection model. Rittenhouse’s method had been adopted. 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., Modern Pharmacy, United Kingdom) at 1.25 mg/kg, along with fentanyl fluanisone (Hypnorm; Janssen, Sanderton, United Kingdom) at 0.5 ml/kg. The hair 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 and their respective vehicle placebos 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), was given orally by gavage in 0.2 ml. This dose was chosen because, in preliminary experiments, it was found to produce peak serum level in the mouse as that reported in humans_23,27,36_ Table 2. 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.

**Table 1. Comparison of peak serum concentrations of the systemic agents used in the mouse and the hamster with those attainable in humans after oral administration.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mouse</th>
<th>Hamster</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg/kg)</td>
<td>Peak serum concn ± SD (µg/ml [range])</td>
<td>Dose (mg/kg)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>200</td>
<td>3.8 ± 2.1 [1.7-7.8]</td>
<td>200a</td>
</tr>
</tbody>
</table>

* Dose used in efficacy tests was 100 mg/kg.
* Reference 27.

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 killed by CO₂ asphyxiation. Hair 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 carry over 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. Published methods used Mupirocin ointment; subsequent studies reported by McLinn, S. A showed that the charcoal method gave similar results when Mupirocin was used in a cream formulation or a laboratory reference powder. 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, UK); 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 (m). In this case, the use of porcine liver esterase (Sigma) was investigated. 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, UK), 3% in O₂-N₂ 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, oral erythromycin at a dose of 100 mg/kg). The doses of erythromycin 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 treatment. 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, and the animals were humanely killed by pentobarbitone overdose. Each lesion and surrounding skin (approximately 5 mm²) 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 erythromycin); and comparator (oral) versus no treatment. Each comparison was made using the 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 Mupirocincream with Mupirocinointment 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 $2.51 \pm 1.69 \log_{10}$ CFU/wound. Therapy with Mupirocin ointment reduced the mean count to $4.62 \pm 2.15 \log_{10}$/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.

**Table 2. Mean bacterial counts from surgical wound infections in the mouse following treatment with Mupirocin cream, Mupirocin ointment and their respective placebos.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean bacterial count (log$_{10}$ CFU/wound) ± SD (no. of wounds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td>Implantation</td>
<td>~5.0</td>
</tr>
<tr>
<td>After 5 days</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>7.23 ± 0.33 (10)</td>
</tr>
<tr>
<td>Placebo cream</td>
<td>7.52 ± 0.40 (10)</td>
</tr>
<tr>
<td>Placebo ointment</td>
<td>7.16 ± 0.43 (10)</td>
</tr>
<tr>
<td>Mupirocin cream</td>
<td>2.51 ± 1.69° (8)</td>
</tr>
<tr>
<td>Mupirocin ointment</td>
<td>4.62 ± 2.15° (8)</td>
</tr>
</tbody>
</table>

° $P < 0.001$ versus respective vehicle placebo and untreated controls.

* $P = 0.01$ versus Mupirocin ointment.

° $P < 0.01$ versus Mupirocin ointment.

Animals that had removed sutures during the treatment period were excluded from the analyses.

In the case of *S. aureus* J1225, Mupirocin cream-treated wounds had a mean count of $1.55 \pm 0.58 \log_{10}$ 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 $2.54 \pm 2.24 \log_{10}$ 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: 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). All active treatments significantly reduced the mean bacterial counts compared with untreated controls (*P* < 0.001 in all cases).

Table 3. 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean bacterial count (log$_{10}$ CFU/wound) ± SD (no. of wounds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>S. aureus J1225</em></td>
</tr>
<tr>
<td>Implantation</td>
<td>Trial 1</td>
</tr>
<tr>
<td>Untreated</td>
<td>7.27 ± 0.23 (10)</td>
</tr>
<tr>
<td>Mupirocin cream</td>
<td>1.89 ± 1.57$(a,b)$ (9)</td>
</tr>
<tr>
<td>Mupirocin ointment</td>
<td>3.49 ± 1.90$(a)$ (8)</td>
</tr>
</tbody>
</table>

*a* *P* < 0.001 versus untreated controls.

*b* *P* < 0.001 versus erythromycin.

*c* Inoculated sites that did not produce lesions were excluded from the analyses. p.o., peroral

(iii) Comparison of Mupirocin cream with Mupirocin ointment.. The mean count for infections with *S. aureus J1225* treated with Mupirocin cream was $1.45 \pm 1.05$ 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 $3.39 \pm 2.11$ log$_{10}$ CFU/wound, with three of the nine evaluable wounds being sterile (trial 2 (Table 4)). In this infection, the effect of Mupirocin cream was not significantly different from that of Mupirocin ointment (*P* > 0.01); 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 $1.34 \pm 0.80 \log_{10} \text{CFU/wound}$ (Table 3). In contrast, Mupirocin ointment reduced the mean count to $3.92 \pm 1.11 \log_{10} \text{CFU/wound}$ 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 $1.90 \pm 1.68$ and $2.56 \pm 1.92 \log_{10} \text{CFU/wound}$, 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.** All wounds treated with Mupirocin cream were devoid ($<10 \text{CFU/wound}$) of the infecting organism, $S. pyogenes$ PA52, as were five of the nine evaluable wounds treated with Mupirocin ointment (mean count, $1.47 \pm 0.66 \log_{10} \text{CFU/wound}$; trial 1 [Table 4]). The efficacies of the Mupirocin formulations and oral $f$ 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).

**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. 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 (m)-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).

Table 4. 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

<table>
<thead>
<tr>
<th></th>
<th>Mean bacterial count (log$_{10}$ CFU/lesion) ± SD (no. of lesions)²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1</td>
</tr>
<tr>
<td>Inoculation</td>
<td>7.46</td>
</tr>
<tr>
<td>After 5 days</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>5.92 ± 0.73 (15)</td>
</tr>
<tr>
<td>Placebo cream</td>
<td>4.46 ± 1.24a (16)</td>
</tr>
<tr>
<td>Placebo ointment</td>
<td>4.56 ± 1.16a (14)</td>
</tr>
<tr>
<td>Mupirocin cream</td>
<td>2.29 ± 0.87a,b (14)</td>
</tr>
<tr>
<td>Mupirocin ointment</td>
<td>3.32 ± 1.02a,c (15)</td>
</tr>
<tr>
<td>Erythromycin, 100 mg/kg (p.o.)</td>
<td>4.60 ± 0.93a (16)</td>
</tr>
</tbody>
</table>

* $P < 0.01$ versus nontreated controls.
* $P < 0.01$ versus placebo.
* $P < 0.01$ versus Mupirocin ointment.
* $P < 0.01$ versus erythromycin

(ii) **Comparison of Mupirocin cream with Mupirocin ointment, oral erythromycin:** Treatment with Mupirocin cream or ointment was significantly more efficacious than with oral erythromycin ($P < 0.01$) (trial 2 [Table 5]). Mean bacterial counts from lesions after all active treatments 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 and in infections such as erysipelas and cellulitis. Impetigo lesions in the hamster bear clinical and histological similarities to those seen in humans and the model has been used to assess various therapeutic regimens. The murine model of skin wound infection is established by implanting contaminated sutures 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, and the data have been shown to correlate well with efficacy in humans. The results showed that the new cream formulation of Mupirocin was as effective as the established ointment preparations. Mupirocin cream was superior to oral erythromycin. 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 and it is reported to the drug of choice in oral treatment of impetigo, that is why it was used as comparator to Mupirocin formulations, but neither systemic agent was as efficacious as Mupirocin cream in the treatment of an experimental staphylococcal impetigo.

Erythromycin is 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. Additional factors limiting the use of
erythromycin are gastrointestinal side effects, 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, supporting the principle that patients are more compliant when given simple and less-frequent dosing regimens. 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 resistances, 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 its candidates. Mupirocin has excellent activity against the major skin pathogens while having little effect on commensals that contribute to the natural defenses of the skin. The unique mode of action of Mupirocin by inhibition of isoleucyl-tRNA synthetase, is thought to be a major contributory factor to its lack of cross-resistance to other antibiotics.

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. Mupirocin also lacks the potential to cause photosensitive irritant reactions and contact sensitization.

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.

Evidence suggests, however, that the delivery vehicle also can influence safety and efficacy.\(^8,9\) For example, Johnson et al\(^{10}\) demonstrated variable toxicity when four topical agents commonly used for wound cleaning were compared in an in vitro model using cultured human fibroblasts.

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

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