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In Vitro and In Vivo Evaluations of the Activities of Lauric Acid Monoester Formulations against *Staphylococcus aureus*

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Due to increasing mupirocin resistance, alternatives for *Staphylococcus aureus* nasal decolonization are needed. Lauric acid monoesters combined with lactic, mandelic, malic, or benzoic acid are being evaluated as possible alternatives. We determined the in vitro activity of 13 lauric acid monoester (LAM) formulations and mupirocin against 30 methicillin-susceptible *S. aureus* (MSSA) isolates and 30 methicillin-resistant *S. aureus* (MRSA) isolates. We then used a murine model of MRSA nasopharyngeal colonization to compare the in vivo activity of mupirocin with three LAM formulations. MSSA and MRSA MIC_{90} values were 0.25 μg/ml for mupirocin and ≤4 μl/ml for all LAM formulations tested. Hsd:ICR mice were challenged with 10^8 CFU/naris MRSA. Five days later, *S. aureus* colonization was documented by culture. Treatment with bland, mupirocin, or one of three LAM ointments was then administered unblinded thrice daily for 2 days. Three days after treatment, both anterior nares were cultured for *S. aureus*. Administration of 128774-49E or 128774-53A was associated with greater eradication of MRSA carriage (24/34 [71%] or 33/40 [83%]) of animals, respectively) than bland ointment (12/38 [32%]) ($P < 0.005$). 128774-53A administration resulted in greater MRSA carriage eradication than mupirocin (19/38 [50%]) ($P < 0.005$) in this model. LAM formulations warrant evaluation for *S. aureus* nasal decolonization in humans.

Nasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) by hospitalized patients has been associated with nosocomial transmission of MRSA (9). Nasal carriage is also recognized as a risk factor for *S. aureus* infection in patients with concomitant human immunodeficiency virus infection, with intravascular devices, undergoing surgical procedures, on hemodialysis or continuous ambulatory peritoneal dialysis, or who have undergone liver transplantation (10, 24, 41, 44). Mupirocin eradicates nasal *S. aureus* carriage in the short term (29). Decolonization of nasal carriers with mupirocin may reduce the incidence of *S. aureus* infections in surgical patients and in those on hemodialysis and continuous ambulatory peritoneal dialysis (35, 45), although this issue is controversial (26).

Mupirocin resistance in *S. aureus* was first reported in 1987, 2 years after mupirocin was introduced into clinical practice (3). Mupirocin resistance in staphylococci has been classified as low-level (MIC, 8 to 256 μg/ml) and high-level (MIC, >256 μg/ml) (13). Low-level resistance results from mutations in endogenous isoleucyl-tRNA synthetase (IleRS) (2, 46), whereas high-level resistance is a result of acquisition and expression of *mupA*, a gene encoding an exogenous IleRS which is not inhibited by mupirocin (19). Widespread use of mupirocin has been accompanied by the emergence of both types of mupirocin resistance in *S. aureus* (27, 31, 38). High-level-resistant strains are not eradicated from the human nasopharynx with mupirocin (1, 3). Harbarth et al. reported a statistically significant association of low-level mupirocin resistance in MRSA with failure of nasal decolonization (18). Others have corroborated this finding (42). Further, the emergence of low-level mupirocin resistance by a glycopeptide-intermediate *S. aureus* strain, as a result of an IleRS mutation (21), in a patient receiving nasal mupirocin (and associated with failed decolonization) has been reported (14). Because of emerging mupirocin resistance in *S. aureus*, alternatives to mupirocin are needed for *S. aureus* nasal decolonization.

The antimicrobial properties of fatty acids have been recognized for many years (12, 22). They have broad-spectrum activity against gram-positive bacteria, including *S. aureus* (12, 22), gram-negative bacteria, such as *Neisseria gonorrhoeae* and *Helicobacter pylori* (7, 8), *Chlamydia trachomatis* (4), enveloped viruses (37), and *Candida albicans* (5). Fatty acids and their monoglycerides have been shown, in an animal model, to be effective vaginal microbicides (30, 36). Fatty acids and their monoglycerides, commonly found in natural products, are considered nontoxic. They contribute to the antimicrobial properties of human milk (37) and skin (28). The Food and Drug Administration has listed fatty acid monoesters as generally recognized as safe (16). The antistaphylococcal activity and minimal toxicity of fatty acids make these formulations potential alternatives to mupirocin for *S. aureus* nasal decolonization.

We determined the in vitro activity against *S. aureus* of 13 lauric acid monoester (LAM) (Table 1) formulations or mupirocin and compared the emergence of resistance to three LAM formulations and mupirocin in *S. aureus*. We also compared the in vivo activity of three LAM formulations with mupirocin for experimental nasal *S. aureus* decolonization in mice using a

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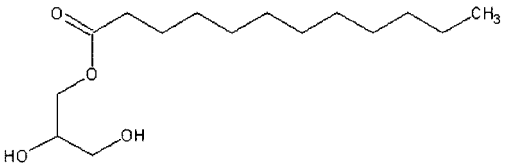
TABLE 1. Lauric acid monoester formulations studied in vitro[a]

Formulation	128774-23												128776-53
	Mandelic acid				Malic acid				Lactic acid				Benzoic acid
	A	B	C	D	E	F	G	H	I	J	K	L	
Lauric acid monoester (%)	1	3	1	3	1	3	1	3	1	3	1	3	3
Organic acid (%)	1	1	0.5	0.5	1	1	0.5	0.5	1	1	0.5	0.5	0.5

[a] Solutions of the lauric acid monoester and organic acid were dissolved in isopropanol. The lauric acid monoester $CH_3(CH_2)_{10}COOCH_2CH(OH)CH_2OH$ has the structure shown below:



modification of a previously described nasal *S. aureus* carriage model (23).

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MATERIALS AND METHODS

Collection of clinical isolates. Thirty clinical isolates each of methicillin-susceptible *S. aureus* (MSSA) and MRSA from the Mayo Clinic (Rochester, MN) and the Cleveland Clinic (Cleveland, OH) collected between January 1985 and December 2002 and stored at −70°C were studied. Five isolates (8%) were from patients with endocarditis, and 16 isolates (27%) were from patients with prosthetic joint infection. The source was not documented for the remaining 39 isolates. One isolate per patient was studied. The isolates were typed using SmaI pulsed-field gel electrophoresis. An isolate of MRSA which we have previously used in other animal models of infection (15) (IDRL-4293, mupirocin MIC, ≤0.125 μg/ml), was studied in vivo.

Mupirocin and LAM formulations. Mupirocin lithium salt powder was purchased from U.S. Pharmacopeia (Rockville, MD). The MICs of 13 LAM formulations (3M Inc., St. Paul, MN) were determined. The concentration of LAM was 1 or 3% wt/wt and each organic acid (lactic, mandelic, benzoid, or malic acid) was 0.5 or 1.0% wt/wt (Table 1). For in vitro studies, solutions of the LAM and organic acid were dissolved in isopropanol (whereas for in vivo studies, formulations were in a petrolatum base). Studies selecting less susceptible isolates in vitro were performed with 128774-23A, 128774-23B, and 128776-53A.

Mupirocin calcium ointment 2% (Bactroban Nasal, SmithKlineGlaxo, Research Triangle Park, NC), and 128774-49D ointment (3% LAM and 1% lactic acid in a petrolatum base), 128774-49E ointment (3% LAM and 1% mandelic acid in a petrolatum base), 128774-53A ointment (3% LAM and 0.5% benzoic acid in a petrolatum base), and bland ointment (petrolatum base) (3M Inc., St. Paul, MN) were studied in vivo.

Determination of MICs. MICs were determined by broth microdilution according to the Clinical and Laboratory Standards Institute guidelines with cation-adjusted Mueller-Hinton broth (MHB) and an inoculum of 10^5 CFU per ml (11). *S. aureus* ATCC 29213 was used as a control strain. For the LAM formulations, six colonies were inoculated into tryptic soy broth; the broth was incubated at 37°C until turbid, diluted to a McFarland standard of 0.5, and then further diluted 1:100 in MHB. MIC testing was performed in microtiter well plates using a total volume of 100 μl containing doubling dilutions ranging from 0.125 to 32 μl/ml of the LAM formulations tested. A well containing no LAM formulation was used as a growth control. Plates were incubated 18 to 24 h in room air at 37C; the MIC was read as the lowest antimicrobial concentration exhibiting no growth.

Selection of less susceptible isolates in vitro. We exposed 5×10^9 CFU of each *S. aureus* isolate to increasing concentrations of mupirocin in 10 ml of MHB containing the following concentrations: 0.125 μg/ml (day 1), 0.25 μg/ml (day 2), 0.5 μg/ml (day 3), 1 μg/ml (day 4), 2 μg/ml (day 5), 4 μg/ml (day 6), 8 μg/ml (day 7), and 16 μg/ml (day 8). Following overnight incubation, the broth culture was centrifuged for 10 min at 900 × g and the pellet was divided into two aliquots. One aliquot was suspended in 10 ml of fresh MHB containing twice the mupirocin concentration of the previous day; the other aliquot was spread on the surface of a Mueller-Hinton agar (MHA) plate containing 4 μg/ml of mupirocin to screen for resistant *S. aureus*. The plate was incubated in room air at 37°C for 48 h. The MIC of 5 to 10 colonies recovered from screening agar was determined at each day of serial passage. This procedure was repeated for 8 consecutive days.

The same procedure (with minor modifications) was used for three LAM formulations. Concentrations of LAM formulations in MHB were doubled each day as follows: 0.25 μl/ml (day 1), 0.5 μl/ml (day 2), 1 μl/ml (day 3), 2 μl/ml (day 4), 4 μl/ml (day 5), 8 μl/ml (day 6), 16 μl/ml (day 7), and 32 μl/ml (day 8). MHB with 20 μl/ml of 128774-23A, 128774-23B, or 128776-53A was substituted for MHA plates due to the insolubility of the LAM formulations in agar (precluding identification of individual colonies). Following overnight incubation, the MHB was subcultured to a sheep blood agar plate and LAM formulation MIC testing was performed on six colonies.

Experimental model of nasal MRSA decolonization. A previously described nasal *S. aureus* carriage model (23) was modified as described below. Healthy 4-week-old 25- to 30-g Hsd:ICR mice housed in "shoebox" cages of five animals each with mouse chow and water available ad libitum were used. The anterior nasopharynx of 10 mice sedated with 60 mg/kg ketamine plus 6 mg/kg xylazine was cultured to assess *S. aureus* carriage. Anterior nasopharyneal specimens were collected by aseptically inserting 7 mm of sterile 6.0 vicryl suture material (hereafter termed swab) into each naris. The swabs were inserted and withdrawn 10 times and then left inserted for 10 min. Both swabs were then placed in a single microcentrifuge tube containing 150 μl of tryptic soy broth and vortexed; 75 μl of tryptic soy broth and both swabs were removed and spread on the surface of a sheep blood agar plate. The plates were incubated at 35°C in 5% CO_2 for 48 h, following which they were inspected for growth. Colonies morphologically resembling staphylococci were tested to determine whether they were *S. aureus* or not using a latex agglutination test (Staphaurex, Lenexa, KS).

We challenged 279 mice with a 10-μl suspension containing 10^8 CFU of MRSA IDRL-4293 pipetted into each naris. This inoculum was shown to result in colonization of 7 of 10 (70%) mice. Five days after challenge, anterior nasopharyngeal cultures were collected. Then the animals were arbitrarily assigned to one of five unblinded treatment regimens consisting of 10 μl of bland, mupirocin, 128774-49D, 128774-49E, or 128774-53A ointment per naris, administered three times daily for 2 days. All mice in a single cage were assigned to the same treatment regimen. The numbers of animals in each treatment group are shown

TABLE 2. Treatment regimen assignment, number of animals successfully colonized, and results of treatment

Treatment	No. of animals challenged	No. of animals colonized before treatment	No. (%) of animals decolonized
Bland ointment	53	38	12 (32)
Mupirocin	56	38	19 (50)
128774-49D	60	39	18 (46)
128774-49E	50	34	24 (71)
128774-53A	60	40	33 (83)

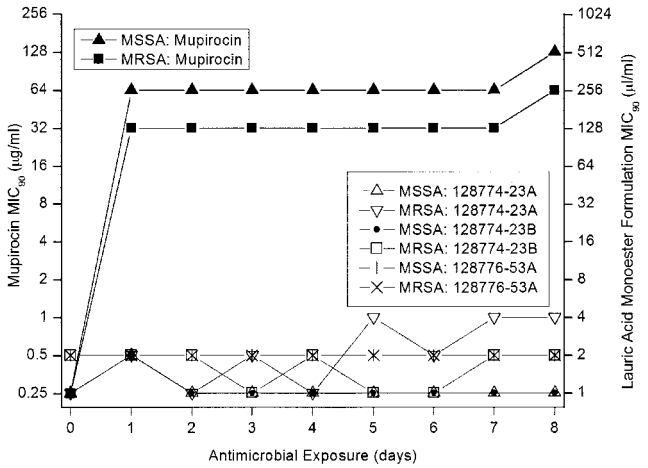

FIG. 1. MIC_{90} values (μg/ml for mupirocin, μl/ml for LAM formulations) of methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* over the days of exposure.

in Table 2. Ointments were administered with a 100-μl glass syringe through a 22-gauge feeding needle (1.25 ball diameters) pushed snuggly against the naris. The ointment-loaded syringe was warmed with a lamp and maintained at 42°C during use (maximum, 10 min) to reduce viscosity and facilitate instillation into the nares. (Maintenance at 42°C for 10 min demonstrated no effect on mupirocin activity in vitro.)

Animals not colonized with *S. aureus* were initially treated (because results of nasopharyngeal cultures performed to detect colonization were not complete until after treatment), but were excluded from the final analysis. Three days after discontinuing treatment, nasopharyngeal cultures for *S. aureus* were performed. Results of treatment were analyzed using Fisher's exact test. We used Bonferoni's correction after comparing the results of five treatment regimens to each other (i.e., 10 tests total); a P value of <0.005 represented a statistically significant difference.

In vivo emergence of resistance. *S. aureus* recovered from mice treated with mupirocin, 128774-49D, 128774-49E, or 128774-53A were tested for susceptibility to the topical agent used for treatment (11).

RESULTS

In vitro studies. There were 18 unique MSSA and 17 unique MRSA pulsed-field gel electrophoresis patterns. MSSA/MRSA MIC_{90} (range) were 0.25 (≤0.125 to 0.5)/0.25 (0.125 to 0.5) μg/ml for mupirocin, 2 (1 to 2)/2 (1 to 2) μl/ml for 128776-53A, 1 (0.25 to 1)/2 (0.25 to 2) μl/ml for 128774-23B, and 2 (0.25 to 2)/4 (1 to 4) μl/ml for 128774-23J. Similar MICs were found for the other LAM formulations and MICs were similar for MSSA and MRSA (data not shown).

After 1 day of in vitro exposure, the mupirocin MIC_{90} values had increased by eight and seven twofold dilutions for MSSA and MRSA, respectively. On subsequent days no further significant changes in the mupirocin MIC_{90} values were detected. After 5 days of LAM formulation exposure, MIC_{90} values had increased a maximum of two twofold dilutions (Fig. 1).

Experimental model of nasal MRSA decolonization. No *S. aureus* was detected from cultures of the 10 healthy, unchallenged animals tested. *S. aureus* was detected in 189 colonization cultures from 279 mice challenged with MRSA (Table 2). The results of treatment are shown as the number of animals decolonized following treatment and the percentage of colonized animals decolonized following treatment. Treatment with 128774-53A or 128774-49E resulted in greater eradication of MRSA carriage than bland ointment ($P < 0.005$). Mupirocin or 128774-49D treatment results were not significantly different than bland ointment treatment results ($P = 0.08$ and 0.14, respectively). 128774-53A treatment resulted in greater MRSA carriage eradication than mupirocin ($P < 0.005$). 128774-49D and 128774-49E treatment results were not significantly different than mupirocin treatment results ($P = 0.46$ and 0.06, respectively).

TABLE 3. Pre- and posttreatment susceptibility results

Treatment	No. of animals	MIC before treatment	MIC range after treatment	No. of mice with resistant[a] *S. aureus*
Mupirocin	19	≤0.125 μg/ml	≤0.125–8 μg/ml	4
128774-49D	21	1 μl/ml	1–8 μl/ml	—[b]
128774-49E	10	2 μl/ml	0.5–4 μl/ml	—
128774-53A	7	1 μl/ml	2–4 μl/ml	—

[a] Defined as mupirocin MIC of ≥4 μg/ml.
[b] —, susceptibility breakpoints not established.

Emergence of resistance. *S. aureus* isolates with mupirocin MICs of ≥4 mg/ml were detected in 4 of 19 (21%) animals failing mupirocin decolonization (Table 3). Animals found to be colonized with mupirocin-resistant MRSA after treatment had not been housed in the same cages. A threefold doubling dilution increase in MIC to 128774-49D was the maximum observed in the animals treated with 128774-49D. The maximum increase in MIC to 128774-53A in the animals treated with this formulation was two doubling dilutions. The maximum increase in MIC to 128774-49E in the animals treated with this formulation was a single doubling dilution.

DISCUSSION

This study shows that mupirocin, 128774-23A, 128774-23B, and 128776-53A and 10 other LAM formulations demonstrate in vitro activity against *S. aureus*. MICs for mupirocin before antimicrobial exposure were similar to those reported previously (17). The MICs of lauric acid monoesters were similar to those reported by Holland et al. (i.e., MIC_{90} of 15 μg/ml and range of 10 to 20 μg/ml in 29 isolates of *S. aureus*) (20), considering that the formulations tested herein contained 1 to 3% lauric acid monoester. In general, the MIC_{50} values of the 3% LAM formulations were one twofold dilution below the MIC_{50} values of the 1% LAM formulations (data not shown). Assuming that LAM is the active component of the formulations, the MIC_{50} of the 3% LAM formulations should be three times lower than that of the 1% LAM formulation; however, we only tested twofold dilutions, so the results were as expected. For this reason, 3% LAM formulations were selected for in vivo testing. Additionally, 128774-53A was chosen for in vivo study because it was expected to be more chemically stable on account of containing benzoic acid, which does not have hydroxyl groups, which might undergo transesterification with the lauric acid ester.

We modified a previously described murine nasal *S. aureus* model (23) to evaluate topical agents being developed for nasal *S. aureus* decolonization. Overall, we achieved staphylococcal colonization in 68% of mice. A cotton rat model of *S. aureus* colonization has recently been used to evaluate lysostaphin

cream, mupirocin ointment, and nisin cream for experimental *S. aureus* nasal decolonization (25). Although the cotton rat model results in a higher nasal colonization rate than does the mouse model used herein, we found no *S. aureus* in unchallenged mice, in contrast to the situation in cotton rat nares (25), making assessment of colonization easier in the mice studied herein. Furthermore, we used a nasal swab in our study, permitting multiple colonization evaluations of the same animal; we analyzed treatment results only from animals with pretreatment cultures positive for MRSA. The cotton rat model and the original mouse model we modified both used nasal excision, which precluded pretreatment microbiological confirmation of MRSA colonization (23, 25).

The LAM formulations studied herein are lipophilic surfactant/emulsifiers. Their exact mechanism of action is unknown but likely involves effects on the bacterial cell envelope and/or induction of autolysin activity and inhibition of protein synthesis. For example, Bergsson et al. demonstrated that *S. aureus* is killed by fatty acids, and especially by monocaprin, through disintegration of the cell membrane, leaving the cell wall intact (6). Ved et al. showed that dodecyl glycerol inhibits peptidoglycan synthesis and stimulates a proteinase which activates peptidoglycan-degrading enzyme autolysin (39, 40). Several investigators have reported effects on toxin synthesis. For example, Schlievert et al. demonstrated that *S. aureus* elaboration of hemolysin, toxic shock syndrome toxin 1, and exfoliative toxin A was inhibited at glycerol monolaurate concentrations below those necessary to inhibit growth (34). Mechanistic studies performed by Projan et al. showed that glycerol monolaurate inhibits synthesis of staphylococcal toxins (and other exoproteins) at the level of transcription by interfering with signal transduction (32). Interference with signal transduction has also been shown in other genera; Rusin and Novick demonstrated that glycerol monolaurate suppresses growth of vancomycin-resistant *Enterococcus faecalis* in the presence of vancomycin and blocks the induction of vancomycin resistance, which involves a membrane-associated signal transduction mechanism, either at or before initiation of transcription (33).

Mupirocin had low in vivo activity in our model. Our study was not, however, designed to demonstrate the efficacy of intranasal mupirocin (as used in humans). There are differences between our model and the administration of intranasal mupirocin to humans. For example, in this study, animals were only treated for 2 days, whereas humans are typically treated for 5 days. There are differences between the anatomy of the nasal passages and types of cells present between humans and mice that may impact on the efficacy of mupirocin in the model described.

We were able to select mupirocin-resistant mutants in vivo and in vitro. It is likely that a mupirocin concentration gradient existed in the nasopharynx of the mice following intranasal mupirocin application, similar to the situation in humans, facilitating selection for mupirocin resistance (43).

In conclusion, our in vitro studies show that mupirocin and 13 LAM formulations are active against *S. aureus*. Two of the three LAM formulations selected for testing in vivo showed activity in a murine nasal *S. aureus* decolonization model. The LAM formulations studied herein, or modifications thereof, may be an alternative to mupirocin ointment for nasal *S. aureus* decolonization in humans.

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