A Randomized Clinical Trial of Mupirocin in the Eradication of Staphylococcus aureus Nasal Carriage in Human Immunodeficiency Virus Disease

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Seventy-six human immunodeficiency virus (HIV)-infected patients with Staphylococcus aureus nasal carriage were randomized to treatment groups receiving intranasal mupirocin or placebo twice daily for 5 days. Nasal cultures for S. aureus were obtained at 1, 2, 6, and 10 weeks after therapy. At 1 week, 88% of mupirocin-treated patients had negative nasal cultures compared with 8% in placebo patients (P < .001). The percentage of mupirocin-treated patients with persistently negative nasal cultures decreased over time (63%, 45%, and 29% at 2, 6, and 10 weeks, respectively) but remained significantly greater than the placebo group (3% at 2, 6, and 10 weeks). In mupirocin-treated patients, most (16/19) instances of nasal recolonization were with pretreatment strains (determined by means of by pulsed field gel electrophoresis); mupirocin resistance was not observed. Five days of treatment with mupirocin eliminated S. aureus nasal carriage in HIV-infected patients for several weeks; however, since the effect waned over time, intermittent dosing regimens should be considered for long-term eradication.

Methods

Population and study design. To be eligible for initial S. aureus nasal carriage screening, HIV-infected volunteers had to be aged >18 years. Exclusion criteria consisted of any of the following: allergic rhinitis or nasal polyps that were treated within the past month, current moderate to severe rhinorrhea, current corticosteroid use, current use of one of several antibiotics (amoxicillin/clavulanic acid, dicloxacillin, nafcillin, cephalaxin, cephradine, cefuroxime, cefaclor, cefixime, ciprofloxacin, clindamycin, gentamicin, rifampin, or vancomycin), pregnancy, and lactation. Patients whose first nasal culture was positive for S. aureus were invited to return for a subsequent culture within 7 days. Those with a second positive culture (stable carriage) were then randomly assigned to a 5-day course of intranasal mupirocin or placebo. Nasal cultures were obtained at 1, 2, 6, and 10 weeks after therapy.

Intervention. Mupirocin was provided as 2% mupirocin calcium ointment in paraffin base (Smith Kline Beecham, Bristol, TN). Placebo was paraffin alone and was similar in appearance. Subjects and staff were blinded to the contents of the tubes. Subjects were instructed to expel a 1-cm length of the ointment (~0.055 g) onto a swab and apply it to their anterior nares bilaterally twice daily...
for 5 days. The nose was to be massaged for 1 min. At the completion of therapy, tubes were weighed to assess compliance, which was defined as use of at least the amount of material required for 20 applications of medication (1.1 g).

Microbiologic evaluation. Nasal specimens were obtained by rotation of a culture swab in each anterior nares. Swabs were then inoculated onto selective mannitol salt agar plates (Difco Laboratories, Detroit, MI). Plates were inoculated at 35°C and were examined at 24 and 48 h. Up to 5 suggestive colonies from the selective plate were then inoculated onto 5% sheep blood agar (Hardy Diagnostics, Santa Maria, CA). Isolates from the blood agar plates were considered to be S. aureus if results on a coagulase test were positive. A latex test (Difco Laboratories, Detroit, MI) was used initially, and, if autoagglutination was present in the control, a tube coagulase test (Difco Laboratories) was performed. Mupirocin-susceptibility testing was performed by disk-diffusion methods according to the National Committee for Clinical Laboratory Standards [10].

The primary outcome was defined as the persistence of nasal cultures that were negative for S. aureus. This was assessed at each posttherapy time point. For the week 1 time point, this required a negative nasal culture at week 1, and, for the subsequent time points, this required a negative nasal culture for week 1 and for all subsequent time points up to and including the time point in question. If a subject missed a follow-up nasal culture appointment, that subject would then become ineligible for the primary outcome at that time point and all subsequent time points. Therefore, a secondary outcome was the percentage of subjects, at each time point, who had a nasal culture positive for S. aureus, irrespective of prior culture results or missed cultures.

Strain typing. Epidemiologic typing was performed by means of pulsed field gel electrophoresis. Chromosomal DNA was prepared as described elsewhere [11], and restriction endonuclease digestion using Smal (Boehringer-Mannheim, Indianapolis) was performed. A sample of isolates was also compared by use of a second endonuclease, Ksp I (Boehringer-Mannheim). Ascertainment of distinct epidemiologic types was performed according to recently established guidelines [12].

Clinical evaluation. At baseline and at days 3 and 5 of therapy, subjects were asked about nasal redness, rhinorrhea, swelling, burning, itching, or dryness.

Statistical analysis. χ² or Fisher’s exact test was used to compare categorical variables, and Student’s t-test was used to compare continuous variables. All analyses were performed with the intention-to-treat principle. Data analysis used blinded treatment labels (A or B). Blinding was broken after data analysis was completed.

Results

Study sample. Of 265 HIV-infected volunteers screened, 76 had 2 consecutive nasal cultures positive for S. aureus within 1 week and were randomly assigned to mupirocin or placebo treatment groups (figure 1). The 2 study groups were evenly balanced according to age (median, 39 years), sex (76% male), and race (all P > .20). Twenty-nine percent of the mupirocin group and 26% of the placebo group were current intravenous drug users (P > .20). Subjects were moderately immunosuppressed (median CD4 lymphocyte counts, 245 and 233 cells/mm³ in the mupirocin and placebo groups, respectively), and several subjects in each group had prior opportunistic infections. In the mupirocin group, 34% were using trimethoprim-sulfamethoxazole prophylaxis, compared with 41% in the placebo group (P > .20). The groups were evenly matched for antiretroviral nucleoside analogue use; only 1 subject (in the mupirocin group) was using protease inhibitors.

Thirty-four (89%) of the subjects in the mupirocin group and 33 (87%) in the placebo group returned medication tubes at the completion of therapy. Nine (26%) mupirocin-treated subjects were not fully compliant (i.e., they used <1.1 g of study medication) compared with 3 (9%) of placebo subjects (P = .11).

Efficacy of mupirocin. At 1 week after completion of therapy, 30 (88%) of 34 evaluable subjects in the mupirocin group had a nasal culture that was negative for S. aureus compared with 3 (8%) of 36 in the placebo group (P < .001). At all subsequent time points, mupirocin-treated subjects were significantly more likely than placebo-treated subjects to have persistently negative nasal cultures (figure 2), although the percentage of subjects in the mupirocin group with persistently negative nasal cultures did diminish over time (29% by week 10). Because assessment of persistence of negative nasal cultures required subjects to have cultures obtained at each time point, subjects who missed appointments at early time points were subsequently not analyzed even if they returned for all later visits. To enable us to evaluate all available cultures at each time point irrespective of the availability of prior cultures, we determined, at each follow-up visit, the percentage of subjects in each group with a nasal culture positive for S. aureus, irrespective of prior culture results or missed cultures.

In the 19 mupirocin-treated subjects in whom nasal recolonization occurred after initial eradication, pulsed field gel electrophoresis after Smal restriction enzyme digestion was used to compare pretreatment and follow-up S. aureus strains. In 16 of 19 subjects, recolonization occurred solely with strains that were present prior to therapy. One subject was recolonized with a new strain; 1 subject was recolonized with a new strain and with his initial strain, and 1 subject was recolonized with 2 new strains in addition to his initial strain. Digestion with Ksp I gave the same results.

Mupirocin resistance and toxicity. In the mupirocin group, testing for mupirocin susceptibility was performed on isolates...
Figure 1. Flow of participants through various stages of a randomized clinical trial of intranasal mupirocin in the eradication of Staphylococcus aureus nasal carriage in human immunodeficiency virus disease. The 113 subjects with a nasal culture positive for S. aureus includes 5 patients who had a negative nasal culture initially but were subsequently found to have a positive culture upon repeat screening and were then reconsidered for the clinical trial.

obtained from all 4 subjects who did not experience eradication of nasal carriage at week 1 and from all 19 subjects who experienced nasal recolonization after initial week 1 elimination. Mupirocin resistance was not found. The most common adverse event was burning or itching, but this did not result in treatment discontinuation and was reported equivalently in the 2 study groups (7.9% in each group).

Discussion

This trial demonstrates that a single 5-day course of intranasal mupirocin eliminates S. aureus nasal carriage in HIV-infected patients for several weeks but that subsequent recolonization is common. That mupirocin is effective in initially eliminating nasal carriage in HIV disease is not surprising, given its utility in other populations [7–9]. It is notable, however, that, after a single course of mupirocin, 71% of health care workers remained free of nasal S. aureus at 12 weeks [13] compared with only 29% of our HIV-infected patients at 10 weeks. This difference illustrates the importance of separate evaluation of therapies in HIV-infected persons.

We believe our study is the first trial of any agent in the eradication of S. aureus nasal carriage in HIV disease. One case series using mupirocin suggested efficacy but was potentially confounded by concurrent treatment with other parenteral agents [14]. There are, however, several limitations to our work. A wide spectrum of participants was enrolled, but we did not have a large enough subgroup of patients at highest risk for S. aureus infection to be certain that mupirocin is as effective in this subgroup as it was in the entire study population. Similarly, although mupirocin resistance did not occur after short-term use, we were not able to evaluate its occurrence with extended use. Resistance has been documented in other populations after long-term use [15], and it is likely that longer-term dosing or perhaps intermittent dosing will be needed for mupirocin to have clinical utility in HIV disease.

Our findings provide a basis for a trial aimed toward evaluation of the efficacy of mupirocin in preventing S. aureus clinical infections in HIV disease. Such a trial would require a much larger sample size and follow-up time, but it could be made optimally efficient if participants were limited to patients at highest risk for S. aureus infections, such as those with, in addition to nasal carriage, an indwelling intravenous catheter, neutropenia, and advanced state of HIV disease [1, 5, 6]. A
trial would also allow determination of the optimal dosing pattern (continuous vs. intermittent) and precise estimation of the emergence of mupirocin resistance with prolonged medication use.

The finding that most instances of recolonization were with endogenous strains indicates that either other *S. aureus* reservoirs (e.g., hands) exist or that our culture technique was not sufficiently sensitive to detect a low level of residual nasal organisms that were not eradicated by treatment. It is the potential presence of extranasal reservoirs that suggests that mere eradication of nasal carriage may not be sufficient to prevent clinical infection. Alternatively, even if extranasal reservoirs do exist, reduction of the overall *S. aureus* burden by eradication of nasal carriage may be sufficient to prevent infection.

Whether mupirocin can prevent *S. aureus* infections in HIV disease remains in question, but decisions must be made nonetheless, both for patients who have a history of *S. aureus* infection and for those who are at high risk. Because mupirocin is the only agent shown to eliminate nasal carriage in HIV disease, it is reasonable to recommend its use. As the effect of a single 5-day course did wane over time, an intermittent dosing regimen (e.g., 5 days per month) is advised during the period of highest risk. The costs of mupirocin and the potential risk of resistance with prolonged mupirocin use, however, demand that its use in a particular patient be continually re-evaluated.

References


