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SHORT REPORT

Efficacy of mupirocin nasal ointment in eradicating *Staphylococcus aureus* nasal carriage in chronic haemodialysis patients

D. L. Holton[1], L. E. Nicolle[2], D. Diley[3] and K. Bernstein[4]

[1,2]*Sections of Infectious Diseases and* [3,4]*Nephrology,* [1,2]*Department of Medical Microbiology and* [3,4]Department of Medicine, *University of Manitoba*

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Summary: Topical 2% mupirocin ointment eradicated chronic *Staphylococcus aureus* nasal carriage immediately post-therapy in 17 (77%) of 22 haemodialysis patients. Mean time to recurrence was 3·8 weeks. Similar pre-therapy and post-therapy phage types occurred in 12 (71%) of 17 patients. *Staphylococcus aureus* infections developed in none of 17 successfully treated patients, two of five treatment failures ($P = 0{\cdot}05$), and 10 of 46 untreated patients studied concurrently ($P = 0{\cdot}03$).

Keywords: Mupirocin; haemodialysis; *Staphylococcus aureus*; nasal colonization.

Introduction

Infection is the second leading cause of morbidity and mortality in haemodialysis patients. *Staphylococcus aureus* is the most significant pathogen, accounting for 70–96% of bacterial infections.[1–3] In a prospective study, Yu *et al.*[4] showed a decreased incidence of *S. aureus* infections if *S. aureus* nasal carriage was eliminated. Until recently, only systemic therapy with either rifampicin or clindamycin reliably eradicated *S. aureus* nasal carriage in haemodialysis patients.[5] These drugs are expensive and may be associated with significant toxicity. Topical gentamicin, vancomycin, bacitracin and oral cloxacillin or tetracycline have interrupted *S. aureus* nasal carriage for less than 2 weeks before relapse occurred.[5]

Mupirocin is a new topical antimicrobial which has been reported to effectively eradicate *S. aureus* nasal carriage in some patient populations[6,7] including haemodialysis patients.[8] Mupirocin reversibly binds to bacterial isoleucyl-transfer RNA synthetase preventing protein and RNA

Correspondence to: Dr D. Holton, Health and Welfare Canada, Laboratory Center for Disease Control, Tunney's Pasture, Ottawa, Ontario, Canada KIA 0L2.

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synthesis.[9,10] It is active against most Gram-positive skin pathogens, although low and high level resistance has been reported.[11–13]

We undertook this pilot study to determine: (a) the efficacy of mupirocin in eliminating nasal carriage in a dialysis population and (b) the length of time patients remained free of nasal *S. aureus* carriage following treatment.

Methods

Population and design

All patients attending an outpatient chronic haemodialysis unit were eligible for enrolment. Sixty-eight patients were screened for the presence of *S. aureus* nasal carriage. Patients with two consecutive nasal swabs, taken at least one week apart, positive for *S. aureus,* were considered to be chronic *S. aureus* carriers and enrolled after obtaining informed consent. No subject was known to be hypersensitive to mupirocin.

Patients applied 2% mupirocin ointment in a paraffin/lanolin base three times daily for 5 days to the internal, anterior medial septa (Little's area) of both nostrils following directions provided by the study nurse. Each patient recorded drug administration and adverse reactions. The study nurse reviewed patient diaries and discussed any adverse drug reactions with each patient. Surveillance of the haemodialysis unit for *S. aureus* nasal carriage was discontinued after study enrolment was completed. A concurrent prospective study documented infectious morbidity and mortality of all patients in the unit throughout the surveillance and study period.

Microbiology

Nasal swabs for *S. aureus* carriage were taken at pre-enrolment, at the first dialysis visit following completion of therapy (end of therapy), weekly for 4 weeks, then monthly for 2 months. Specimens were transported to the laboratory in Amies transport media, inoculated onto 5% sheep blood agar and 10% mannitol salt agar plates, and incubated aerobically at 37°C for 48 hours. Gram-positive coagulase positive cocci isolated from the blood agar plate were identified as *S. aureus*. Oxacillin disc (1 mg, BDL) sensitivities were performed on all *S. aureus* isolates. Isolates growing within 13 mm of the oxacillin disc were inoculated onto Mueller Hinton plates containing 6 mg l^{-1} oxacillin to verify methicillin resistance. Mupirocin susceptibility was determined by Kirby-Bauer agar disc method (1 μg disc). *Staphylococcus aureus* isolates were phage typed by the Laboratory Center for Disease Control, Ottawa, Canada.

Definitions and data analysis

Patients were considered cured if *S. aureus* was not isolated in any post-therapy cultures. If *S. aureus* was isolated on the first nasal swab obtained after completion of therapy, patients were designated failures. Patients relapsed when the *S. aureus* strain isolated post-therapy did not

differ by more than two phage types from the pre-therapy isolate and were considered recolonized if the post-therapy strain differed by more than two phage types. Patients with non-typable strains isolated both pre-therapy and post-therapy were considered relapses. Analysis was performed using the χ^2-square test.

This phase two trial was approved by the University of Manitoba, Faculty Committee on Human Subjects in Research and the Health Sciences Centre Research Committee.

Results

Twenty-two (32%) of 68 patients in the haemodialysis unit were identified as *S. aureus* nasal carriers during the 70-day surveillance study which preceded the mupirocin trial. All 22 patients were enrolled in the trial. Twelve different phage types were identified in these 22 patients. Seventeen (77%) patients were culture negative at the end of therapy. The mean time to recurrence for those negative at the end of therapy was 3·8 weeks. Ten (46%) patients remained culture negative 4 weeks post-therapy, seven (32%) at 2 months, and five (23%) at 3 months. The positive nasal carriers at 3 months included five (23% of total) failures of therapy, seven (32%) relapses and five (23%) recolonized. Thus, similar pre- and post-therapy phage types occurred in 12 of 17 (71%) patients not cured. All pre- and post-therapy *S. aureus* isolates were susceptible to mupirocin. The single subject with a pre-treatment methicillin-resistant *S. aureus* isolated was a treatment failure.

Therapy was well tolerated. Three (13%) of 22 patients complained of mild nasal itching. Although one of these patients missed three doses, the course of therapy was subsequently completed. An additional patient missed four doses for unknown reasons. *Staphylococcus aureus* nasal carriage recurred in both of these patients, one as a relapse, and one recolonized.

None of the 17 patients who were culture negative at completion of therapy developed *S. aureus* infections during the three months follow-up. *Staphylococcus aureus* cellulitis was observed, however, in two (40%) of five patients who failed therapy ($P = 0{\cdot}05$). Ten (22%) of 46 patients not enrolled in the study but followed concurrently had *S. aureus* infection ($P = 0{\cdot}03$). These 10 infections included three fistula site infections, three episodes of sepsis, two pneumonias, and one each of cellulitis and soft tissue infection.

Discussion

These observations contrast with the report of Chow & Yu[5] who found less than 25% of patients using topical agents such as gentamicin, vancomycin or bacitracin remained culture negative 3–14 days after completing treatment. Our results are, however, similar to the observed response to

systemic therapy. Yu *et al.*[4] found 75% of patients remained culture negative after combined therapy with oral rifampicin and topical bacitracin 1 month after therapy, but most patients had positive nasal cultures for *S. aureus* by 3 months after therapy. Boelaert *et al.*[8] have also recently reported that continuously administered mupirocin eradicated *S. aureus* nasal carriage in haemodialysis patients and was associated with a decreased incidence of *S. aureus* infections. Although they reported no mupirocin resistance, the continual administration of drugs would likely increase the potential for resistance to develop. Our study suggests that the intermittent use of mupirocin may also be effective in eradicating *S. aureus* carriage in haemodialysis and is associated with a significant decrease in *S. aureus* infections.

We observed a higher relapse rate and lower recolonization rate than was observed in a study using a 5-day course of mupirocin to eradicate chronic *S. aureus* nasal carriage in a group of 32 healthy subjects. Casewell & Hill[6] found 10 (71%) of 14 patients recolonized and four (29%) relapsed during 22 weeks of follow-up. These authors postulated that patients who relapsed were colonized with *S. aureus* at other sites. This hypothesis may explain why our patients had a higher rate of relapse. Compared to healthy controls, haemodialysis patients have twice the rate of *S. aureus* skin colonization.[14–16] *Staphylococcus aureus* skin colonization has recently been correlated with personal hygiene in haemodialysis patients.[17] As this study did not include any evaluation of personal hygiene, it is not known whether the patients who failed had poorer personal hygiene. The level of personal hygiene may be relevant to the two patients who developed *S. aureus* infections after failing to eliminate *S. aureus* nasal carriage.

This preliminary information suggests that a prospective, randomized placebo-controlled trial to determine efficacy and cost benefit of mupirocin in this population is warranted.

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