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Original Article

Nasal mupirocin ointment decreases the incidence of *Staphylococcus aureus* bacteraemias in haemodialysis patients

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Abstract. The incidence of *S. aureus* bacteraemia in a haemodialysis unit was studied over 2 years (167.75 patient-years of follow-up) during which nasal calcium mupirocin was used to eradicate nasal *S. aureus* carriage; this incidence was compared to that previously observed in the same unit before the use of nasal mupirocin (185.8 patient-years). Nasal mupirocin led to eradication of nasal *S. aureus* carriage in 96.3% of surveillance cultures and to a fourfold reduction in the incidence of *S. aureus* bacteraemia per patient-year, from 0.097 before mupirocin to 0.024 with mupirocin use ($P=0.008$). Once or thrice weekly maintenance regimens of mupirocin were equally efficacious. The incidence of bacteraemia caused by other micro-organisms was not significantly affected. One single mupirocin-resistant isolate was identified in a nasal surveillance culture. Eradication of *S. aureus* from the nares did not lead to overgrowth by other micro-organisms. Chemoprophylaxis with nasal mupirocin in haemodialysis patients is cost-effective.

Key words: bacteraemia; haemodialysis; infection; mupirocin; nasal carriage; *Staphylococcus aureus*

Introduction

Infection remains a major cause of morbidity and the second cause of mortality in patients on maintenance haemodialysis [1,2]. Most of these infections are of bacterial origin, *Staphylococcus aureus* being the micro-organism most commonly implicated [1–4]. The key role of nasal carriage of *S. aureus* in the pathogenesis of subsequent infections caused by this micro-organism is now well established [5]. This has been shown in patients on haemodialysis as well as in those on continuous ambulatory peritoneal dialysis [3,5–7]. Two regimens, oral rifampicin combined with nasal bacitracin [3] and nasal calcium mupirocin [7], have been shown to eradicate nasal carriage of *S. aureus* in haemodialysis patients. The present study shows that the long-term use of nasal mupirocin in *S. aureus* carriers significantly decreases the incidence of bacteraemia caused by *S. aureus* in a haemodialysis unit.

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Subjects and methods

Study design

Between 1 October 1989 and 30 September 1991 all patients on maintenance haemodialysis in one single dialysis unit were screened for nasal carriage of *S. aureus*. The methods for culturing the nares, for the isolation and identification of *S. aureus*, for the determination of the minimal inhibitory concentration (MIC) of oxacillin and mupirocin, and for bacteriophage typing of *S. aureus* were as previously reported [7]. *S. aureus* strains were also evaluated by restriction endonuclease digestion of plasmid DNA with EcoRI and Hind III [8]. Patients were considered carriers if two swabs of the anterior nares, taken one week apart, were positive for *S. aureus*. All carriers, after giving their consent, were treated with 2% calcium mupirocin in a white soft paraffin base (Bactroban nasal). During the first 5 days the ointment was applied to the anterior nares three times daily. Subsequently patients were treated at the end of each haemodialysis session (= three times weekly) for the first 6 months of the trial and only once weekly at the end of a haemodialysis session for the 18 subsequent months of the trial. Approximately 1 cm of ointment was applied by an applicator to the anterior nostrils, which were then massaged. Repeat cultures were obtained from the nares of patients receiving mupirocin at months 3 and 6 and at monthly intervals during the subsequent 18 months. Patients who were not carriers when first evaluated were cultured every 3 months and those who became carriers were enrolled in the mupirocin trial. No patient received mupirocin for cutaneous application.

The patients were followed prospectively for the development of bacteraemia. When a patient presented with fever >38°C with or without other signs of infection, three pairs of blood cultures were collected using a standard aseptic technique. Blood culture isolates of *S. aureus* were considered

relevant if grown from more than two of the six culture bottles. The incidence of bacteraemia caused by *S. aureus* and by other micro-organisms in the total haemodialysis population over the 2 years of the study was compared with the incidence of bacteraemia during a prior 2-year period (October 1986–September 1988) when mupirocin was not being used, as previously reported [4]. In the pre-mupirocin study, bacteraemic episodes occurring within the first months of haemodialysis were not reported [4]; however, they were included for present comparison.

To determine whether patients treated with mupirocin became colonized with Gram-negative rods and/or yeasts, surveillance nasal cultures were taken twice. Nasal swabs were taken simultaneously from 30 patients who had been treated with nasal mupirocin for more than 6 months and, for comparison, from 30 haemodialysis patients who had never been treated with mupirocin. Swabs were plated on Columbia agar with 5% sheep blood (Becton–Dickinson), MacConkey agar (bioMérieux) and Sabouraud agar supplemented with gentamicin 0.1 g/l and chloramphenicol 0.05 g/l (bioMérieux) and cultures were incubated at 35°C. The presence or absence of Gram-negative organisms and yeasts was noted after incubation for 48 h and 5 days respectively.

One single *S. aureus* strain, which was resistant to mupirocin (MIC > 512 μg/ml), was studied by Southern blot analysis and hybridization of total DNA with a gene probe specific for mupirocin resistance [9]. All *S. aureus* nasal cultures from this patient were ribotyped for epidemiological investigation [10].

Cost-effectiveness

The cost of treatment of *S. aureus* bacteraemias for the 2-year period before the mupirocin study was compared with the combined cost of treatment and prophylaxis during the 2 years of the mupirocin study. During the pre-mupirocin period, the cost included the treatment of *S. aureus* bacteraemia (cost of hospitalization, diagnostic investigation, and drug treatment). During the 2 years of the mupirocin study, the cost included, in addition, that of nasal cultures (assuming the need for surveillance cultures every 3 months) and of mupirocin ointment (assuming the use of one 3-g tube every 2 months in carriers, at the present price in UK). Costs, in USA $ (1 USA $ = 35 Belgian francs), are expressed per patient-year at risk.

Statistical analysis

The characteristics of the patients in the two 2-year periods were compared by contingency table analysis. The incidence of bacteraemia in the two study periods was compared by the Chi-square test (2 × 2 tables, using Yates' correction).

Results

During the 2 years of the study, 150 patients with chronic renal failure were treated by maintenance haemodialysis for a total of 167.75 patient-years. Eighty-six patients (57.3%) had two successive nasal cultures, taken at a 1-week interval, which were positive for *S. aureus*. These patients were considered stable nasal carriers and were enrolled in the open mupirocin trial. Six patients received mupirocin for less than 2 weeks and were therefore not evaluable (3 patients died, 1 changed to CAPD treatment, 1 moved to another dialysis centre, and 1 discontinued dialysis). Eighty assessable patients received nasal mupirocin for 82.83 patient-years (thrice weekly for 16.75 and once weekly for 66.08 patient-years). The duration of mupirocin treatment averaged 12.3 ± 8.2 (SD) months per patient. The calcium mupirocin ointment was tolerated well by all patients.

All *S. aureus* strains were sensitive to oxacillin. A total of 792 surveillance nasal cultures were obtained from 80 patients treated with mupirocin. Only 29 of 792 (3.7%) cultures from 17 of 80 patients (21.2%) yielded *S. aureus*. All positive cultures were obtained during weekly treatment (0/60 cultures were positive during thrice-weekly treatment compared with 29/732 cultures during once-weekly treatment). For 16 of the 17 patients, the strains obtained before treatment were compared by phage typing and plasmid pattern analysis with the strains isolated during the course of therapy. Seven of the 16 patients (43.7%) were subsequently recolonized with strains that were identical by plasmid pattern analysis. One of these patients was recolonized later by a different strain. Therefore only 8.8% of the 80 patients treated with mupirocin were transiently recolonized with strains that were identical by plasmid pattern analysis with the pretreatment strains. Eight of the 16 patients were recolonized transiently with strains that by phage typing were identical to the pretreatment strains. Two patients were colonized pre- and post-treatment with strains that were non-typable by phages. In five cases the plasmid pattern analysis and phage typing results were discrepant. In four of those cases, plasmid pattern analysis discriminated between the strains but phage typing did not.

Among the 29 strains of *S. aureus* recovered from subsequent surveillance cultures of the nares, only one mupirocin-resistant strain was found (isolate at 19 months). This strain was highly resistant to mupirocin (MIC > 512 μg/ml). Hybridization studies with a gene probe specific for mupirocin resistance confirmed that this isolate carried the gene for high-level mupirocin resistance. Phage typing, plasmid typing, and ribotyping studies confirmed that this strain and the one isolated 2 months earlier were identical but were different from the *S. aureus* nasal strain obtained before mupirocin treatment. Mupirocin was stopped and a 5 day-course of oral rifampicin 300 mg t.i.d. and nasal bacitracin ointment q.i.d. eradicated staphylococcal carriage.

The incidence of *S. aureus* bacteraemia was calculated for the entire group of 150 patients, including non-carriers and carriers (the carriers received mupirocin). Four episodes of *S. aureus* bacteraemia, each in a different patient, occurred during the total follow-up of 167.75 patient-years, giving an incidence rate of 0.024. The incidence of bacteraemia was the same with mupirocin three times per week (1 episode per 44.08 patient-years = 0.023) as with mupirocin once a week (3 episodes per 123.67 patient-years = 0.024). In only

one of the four cases was a nasal culture, taken at the time of the bacteraemic episode, positive for *S. aureus*. The *S. aureus* strains isolated from blood and from the surveillance nasal cultures from three of those patients were evaluated by bacteriophage typing and plasmid analysis. For two patients, the blood isolate was identical to the nasal strain obtained before or at the time of infection. The blood isolate from the third patient differed from the initial nasal strain but was identical to the strain isolated at the time of bacteraemia from the exit site of a central venous haemodialysis catheter.

Table 1 compares the incidence of bacteraemia during the 2 years of mupirocin use (present study) versus that observed during a prior 2-year period in which mupirocin was not used. About half of the patients in the present trial (71/150) had also participated in the previous study without mupirocin [4]. Patient characteristics were similar in both study periods, although the proportion of patients with a serum ferritin > 1000 µg/l was lower in the present study ($P = 0.052$). With the use of mupirocin, the incidence of bacteraemia caused by *S. aureus* decreased from 0.097 to 0.024 ($P = 0.008$), whereas the incidence of bacteraemia caused by other micro-organisms was not significantly affected ($P = 0.3$). *S. aureus* caused 18 of 33 bacteraemic episodes (54.5%) prior to mupirocin, but only four of 23 episodes (17.4%) with the use of mupirocin. In the pre-mupirocin period, therapy of 18 episodes of *S. aureus* bacteraemia required 434 days of hospitalization (0.64% of total follow-up) and cost $166 477 (mean cost $9249 and median cost $3429 per episode), corresponding to $896 per patient-year at risk. During the mupirocin period, hospitalization for *S. aureus* bacteraemia was reduced to 74 days (0.12% of total follow-up time) and the cost was reduced to $164 per patient-year at risk (5-fold reduction). Adding the cost of prophylaxis ($32 for a nasal culture every 3 months and $35 for nasal calcium mupirocin ointment once a week to 57.3% of the haemodialysis population) results in a cost saving of $665 per patient-year on haemodialysis.

Nasal cultures for Gram-negative rods and for yeasts were performed twice in 30 haemodialysis patients who had received nasal mupirocin for > 6 months: only two cultures (2/60 = 3.3%) were positive, one for *Acinetobacter boumanii* and one for *Candida parapsilosis*. In a control group of 30 haemodialysis patients who had never received mupirocin, three cultures (10%) were positive, each for *Klebsiella oxytoca* (no significant difference).

Discussion

The present study confirms the high prevalence (57.3%) of *S. aureus* nasal carriage in haemodialysis patients. Several studies have underlined the importance of nasal carriage in the subsequent development of *S. aureus* infections in this patient population [3,5,7,11]. We have previously shown by bacteriophage typing and analysis of plasmid DNA that *S. aureus* strains causing infections in these patients usually (in 85% of cases) are similar to those persistently carried in their nares [11]. Several placebo-controlled studies have demonstrated that nasal calcium mupirocin ointment eradicates nasal

Table 1. Comparison of the incidence of bacteraemia prior to and with mupirocin treatment

	Prior to Mupirocin ($n = 158$)	Present study ($n = 150$)	P
Patient characteristics			
Characteristics at inclusion			
age > 65 years (%)	38	43.3	NS
duration of haemodialysis: > 3 years (%)	29	30	NS
Follow-up (%) with			
diabetes	10.9	15.8	NS
serum ferritin > 1000 µg/l	19.0	11.2	0.052
central venous haemodialysis catheter	3.2	5.0	NS
Incidence of bacteraemia			
No. of episodes/no. of patient-years	33/185.8	23/167.75	
caused by			
S. aureus	18	4	
other micro-organisms	15	19	
Incidence of bacteraemia per patient-year			
caused by			
S. aureus	0.097	0.024	0.008
other micro-organisms	0.081	0.113	NS
Cost of treatment of *S. aureus* bacteraemia per patient-year at risk (USA $)			
Treatment	896	164	
Prophylaxis			
nasal surveillance cultures	0	32	
mupirocin ointment	0	35	
Total	896	231	

S. aureus carriage in healthy individuals [12–15]. In a previous study, also placebo-controlled we confirmed the efficacy of mupirocin in haemodialysis patients with nasal carriage of *S. aureus*. In this study, which lasted 9 months, the number of *S. aureus* infections was significantly reduced in the mupirocin-treated group [7]. In view of this result, the inclusion of a placebo group was not felt to be justified for the present evaluation. The aims of the present study were threefold. First, to study the long-term (2 years) effectiveness of nasal mupirocin for suppressing nasal carriage and reducing the incidence of *S. aureus* bacteraemia in haemodialysis patients. Second, to quantify the risk of emergence of mupirocin-resistant strains during long-term chemoprophylaxis. Third, to study the cost-effectiveness of this chemoprophylactic strategy.

Nasal mupirocin suppressed *S. aureus* carriage very efficiently: only 3.7% of the 792 surveillance nasal cultures yielded *S. aureus* during the 2 years of the study. In addition, only 8.8% of the 80 patients treated were transiently recolonized with strains identical to pretreatment strains by plasmid pattern analysis. Only 10% of the patients were recolonized by strains that by phage typing were identical to the pretreatment strains.

Discrepancies between plasmid pattern analysis and phage typing have been noted previously [16–19]. In general, comparative studies have shown plasmid pattern analysis to be more discriminatory [16–19].

In only one of the 80 patients on mupirocin was recolonization of the nares due to a strain that was mupirocin-resistant and carried the gene for high-level mupirocin resistance [9]. As reviewed by Cookson, several studies have documented the occurrence of resistance to mupirocin during therapy with this agent [20]. However, many of the resistant strains had MICs between 34 and 64 μg/ml (low level of resistance), the clinical relevance of which is unclear, given the topical concentration of 20 000 μg/ml. Furthermore, most were from patients using mupirocin for dermatological conditions. After using nasal mupirocin in our haemodialysis unit for 108 patient-years (including the 82.83 patient-years of the present study), we identified only one strain of mupirocin-resistant *S. aureus*. Although reassuring, these data await confirmation by other groups.

Suppression of nasal staphylococcal carriage by mupirocin reduced the incidence of *S. aureus* bacteraemia (0.024) fourfold, when compared to a historical control period in the same dialysis unit, prior to the use of mupirocin (0.097). Although the incidence of recolonization was higher during once-weekly than during thrice-weekly mupirocin, the incidence of *S. aureus* bacteraemia was similar, whether maintenance application of mupirocin was done three times a week (incidence of 0.023) or once a week (incidence of 0.024). Patient characteristics were similar in the historical control group and the mupirocin-treated group. However, due to the widespread use of erythropoietin, fewer patients in the mupirocin period had iron overload (serum ferritin > 1000 μg/l). Although a decreased prevalence of iron overload could have led to a decreased incidence of bacteraemia [4], the decrease in incidence of bacteraemia during the mupirocin period was limited to *S. aureus*, whereas the incidence of bacteraemia caused by other micro-organisms did not decrease. This specificity points to a direct effect of nasal mupirocin.

Casewell and Hill have shown that the nasal flora of healthy carriers was not replaced by other micro-organisms during 5 days of treatment with nasal mupirocin [12]. The present study confirms this result in haemodialysis patients who had received nasal mupirocin for more than 6 months.

The high cost of treatment of *S. aureus* bacteraemia (mean of $9249 and median of $3429) is consistent with the cost of $6000 for treating an episode of nosocomial bacteraemia, reported by Maki *et al.* [21]. A fourfold decrease in the incidence of *S. aureus* bacteraemia with the use of mupirocin led to a fivefold decrease in hospitalization requirement and cost for treatment of *S. aureus* bacteraemia. Even after adding the cost of surveillance nasal cultures and of nasal mupirocin ointment, nasal mupirocin chemoprophylaxis is cost-effective in the haemodialysis setting.

In conclusion, the results of this study indicate that long-term nasal mupirocin, by virtually eliminating nasal *S. aureus* carriage, has a significant effect on the incidence rate of *S. aureus* bacteraemia in a patient population known to be at high risk of this infectious complication. Mupirocin chemoprophylaxis is cost-effective. Furthermore, when mupirocin is used as described in this study, the incidence of resistant strains is low (one resistant isolate over 108 patient-years). There is an urgent need to compare several prophylactic strategies in haemodialysis patients. The systematic use of nasal mupirocin at a maintenance interval of once a week in all identified *S. aureus* carriers on haemodialysis (as in the present study) should be compared with the use of mupirocin by a subgroup of *S. aureus* nasal carriers who are at particularly high risk of bacteraemia. Such patients could include dialysis patients with a history of *S. aureus* infection and those dialysed through central venous catheters [22]. Moreover, the risk of *S. aureus* infections should be compared in dialysis patients with intermittent versus continuous *S. aureus* nasal carriage.

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