Cost-effectiveness of prophylactic nasal mupirocin in patients undergoing peritoneal dialysis based on a randomized, placebo-controlled trial

Peter Davey, Ann-Marie Craig, Cathy Hau and Mo Malek

The study objective was to measure the benefits of elimination of nasal carriage of Staphylococcus aureus by calcium mupirocin ointment in patients undergoing continuous ambulatory peritoneal dialysis. The design was a prospective, placebo-controlled, randomized clinical trial. The subjects were 267 patients recruited from nine renal units in Belgium, France and the UK. The main outcome measures were the rate of catheter exit site infection (ESI), rates of other infections and healthcare costs from the perspective of a hospital budget-holder. The rate of ESI caused by S. aureus was significantly reduced from one in 28.1 patient months to one in 99.3 patient months (P = 0.006) and there were also non-significant trends towards lower rates of ESI caused by any organism and peritonitis caused by S. aureus. In comparison with the placebo group, patients in the mupirocin group with ESI had lower antibiotic (P = 0.02) and hospitalization costs (P = 0.065). However, overall costs of antibiotic treatment, for all infections combined, were not significantly different (P = 0.2) and total antibiotic costs (including mupirocin) were significantly higher in the mupirocin group (P = 0.001). Mupirocin prophylaxis would have been cost-neutral if the rate of ESI increased to >75% in the placebo group, or if all healthcare costs increased by 40%, or if the cost of screening was reduced from £15 to £3 per patient, or if the cost of mupirocin treatment was reduced from £93 to £40 per patient year. In conclusion, savings in healthcare costs are unlikely to be sufficiently great to offset the cost of mupirocin and screening for nasal carriage of S. aureus. The decision about whether or not to implement mupirocin should depend on a local analysis of the value of preventing ESIs caused by S. aureus.

Introduction

Staphylococcus aureus and Staphylococcus epidermidis are the bacteria which most frequently cause peritonitis, exit site infection (ESI) and tunnel infection in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). ESI, which is an established risk factor for peritonitis, is more commonly caused by S. aureus than S. epidermidis (64% versus 14%). Peritonitis is the most severe of these infections and may result in hospitalization, loss of the dialysis catheter and prolonged antibiotic therapy. An average of 43% of CAPD patients are nasal carriers of S. aureus (range 17–51%) and recent studies have shown a relationship between nasal carriage of S. aureus and subsequent development of S. aureus ESI, tunnel infection and peritonitis. After application of mupirocin for 5 days, there is approximately 97% eradication of nasal carriage of S. aureus and, in comparison with historical controls, a reduction in the risk of ESI and peritonitis caused by S. aureus. The aim of this study was to measure the benefits of elimination of nasal carriage of S. aureus by calcium mupirocin ointment in patients undergoing CAPD. Data about clinical effectiveness have already been published. This paper reports the results of an economic evaluation conducted alongside the clinical trial.

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Materials and methods

Study design

The primary outcome measure was the rate of infective complications, particularly ESI. Secondary outcome measures were the incidence of other infections, the frequency of catheter removal and the healthcare costs of management of infections. The perspective of the economic analysis was restricted to hospital costs; no attempt was made to measure community healthcare costs, indirect social costs or intangible costs.

The study was a randomized placebo-controlled double-blind comparative trial conducted at nine different centres in the UK, France and Belgium. Clinical and microbiological results have already been published.\(^6\)

Patients received repeat courses of either placebo or calcium mupirocin ointment every month, for a period of up to 18 months. A n amount of ointment equivalent to the size of a match-head was applied to each nostril twice daily for 5 days each month. Patients visited the clinic at 2-monthly intervals and were given two tubes of ointment.

Patient inclusion

The study protocol was approved by the ethics committee in each participating hospital. Patients were eligible for inclusion if they were >18 years, were new or established CAPD patients, were nasal carriers of S. aureus and were willing and able to comply with the study protocol. All patients gave written informed consent.

Exclusion criteria were: known allergy to mupirocin, white soft paraffin or glycerine ester; pregnancy or breast feeding; antibiotic treatment for CAPD-related infection within 1 month of randomization; symptoms or signs of active CAPD-related infection at the time of randomization; intra-nasal or topical mupirocin in the previous 6 months; chronic eczema or psoriasis which required regular treatment with topical steroids, coal-tar products or Dithranol and receipt of investigational new drugs within the 3 months before randomization.

Definition of infection

Exit site infection was defined as peri-catheter erythema of \(>2\) mm and/or exudate with or without a positive culture. Tunnel infection was defined as erythema, oedema or tenderness of the subcutaneous tunnel, with or without discharge or positive culture. Peritonitis was defined as a dialysate leucocyte count of \(>100\) cells/mm\(^3\) when \(>50\%\) of those cells were polymorphonuclear leucocytes.

Infections were categorized as 'ESI-only' if there was no clinical evidence of either infection of the catheter tunnel or peritonitis. Patients were classified as 'ESI with other' if they had ESI but also had either tunnel infections or peritonitis during the period of study observations. Finally, patients were classified as 'other' if they received antibiotics for tunnel infection or peritonitis but had no evidence of ESI throughout the period of study observation. The additional hospitalization associated with infection and the incidence of catheter loss were also recorded.

Statistical methods

Individual patients could have more than one infection during the period of study. The risk of infection per patient year was analysed with a negative binomial analysis (mixed effects model). Proportions and their differences were compared by calculation of odds ratios with 95% confidence intervals (CI). Healthcare costs were analysed with both non-parametric and parametric methods. The median is the cost incurred by at least 50% of the sample, whereas the mean is influenced by outlying patients with unusually high costs, therefore the mean is a better guide to total cost over a period of time. For comparison, a point estimate of the difference in medians was made (using Minitab for Windows, release 10). This is an estimate of the difference in the medians of the population from which the samples were derived, it is not the same as the difference between the sample medians. The statistical significance of differences in healthcare costs was analysed by a non-parametric method (Mann-Whitney test for overall costs and Cochran-Mantel-Haenszel for costs stratified by country). Simulations for the sensitivity analysis were done with a program written in GLIM (generalized linear interactive model).

Identification, measurement and valuation of healthcare costs

Data about protocols for infection management were obtained from clinicians at eight of the centres in order to identify data to be collected in the trial. All study centres had protocols for antibiotic treatment of exit site or tunnel site infections and peritonitis. Six centres routinely performed serum drug assays for patients receiving iv vancomycin and only one centre routinely performed assays for patients receiving intra-peritoneal aminoglycosides. None of the centres had special procedures for isolation of patients with suspected or confirmed infections, and all centres used only simple gauze dressings for ESIs or tunnel site infections.

Measurement of costs in the trial was restricted to the following variables: therapeutic antibiotics administered (unit dose, route of administration, doses per day and duration), replacement of intraperitoneal catheters and additional days of hospitalization for infection management.

The majority of drugs in the study were available in the UK and priced using the March 1994 version of MIMS (Monthly Index of Medical Specialities; Galleon Ltd, UK and priced using the March 1994 version of MIMS (Monthly Index of Medical Specialities; Galleon Ltd,
Cost-effectiveness of mupirocin prophylaxis in CAPD

Woking, U.K.). Some antibiotics were only available in specific countries, most notably Belgium, therefore their respective prices were taken from the Repertoire Commenté des Médicaments 1993 and converted into £ sterling using the exchange rate given in the Financial Times of 3 May 1994. The estimated cost per hospital bed day (£246) was the average cost across the eight study centres.

Calculation of incremental cost per infection avoided by screening and prophylaxis

Each patient was screened with three nasal swabs and was classed as a carrier of S. aureus if at least two of these swabs were positive. The estimated cost of nasal swabs was £15 for each patient on CAPD. The annual cost of mupirocin prophylaxis at the doses used in the trial is £93.

For the incremental analysis, the patients were divided into four groups: non-carriers, carriers with no infection, carriers with ESI and carriers with other infection. Carriers were further sub-divided into those who received mupirocin or placebo. For each infection group, the average cost of infection management per patient year was calculated by multiplying the probability of being in each infection group by the mean cost per patient. For the mupirocin and placebo groups a total expected average cost of infection management was then calculated by summing the average cost for each infection group. The incremental cost of using mupirocin was calculated from the difference in total expected average cost of infection (mupirocin patients – placebo patients). The incremental effectiveness was calculated from the difference in probability of staphylococcal ESI (placebo patients – mupirocin patients). The incremental cost-effectiveness was calculated by dividing incremental cost by incremental effectiveness.

Results

Effectiveness

Between December 1990 and April 1993 a total of 1144 patients were screened for nasal carriage of S. aureus in order to identify 267 (23.3%) nasal carriers of S. aureus, of whom 134 were randomized to receive calcium mupirocin and 133 received a placebo. The mean age was 60.3 years and males outnumbered females by 3:2 in both groups. Just over half of the patients (52%) were recruited from UK centres. A total of 113 patients had one or more infections during the period of observation within the trial (Table I). There were no significant differences in the number of patients with infection but the total number of infections and the number of infections per patient tended to be higher in the placebo group, particularly for ESI alone or with other infections (Table I).

The rate of ESI caused by any organism (including S. aureus) was one in 22.5 patient months in the control group versus one in 42.1 patient months in the mupirocin group (P = 0.17) and the rate of ESI caused by S. aureus was significantly reduced from one in 28.1 patient months to one in 99.3 patient months (P = 0.006). There was also a small, but not statistically significant reduction in the rate of S. aureus peritonitis (from one in 53.8 patient months to one in 81.8 patient months).

Cost of treatment of infections. It proved impossible to identify precisely the antibiotics prescribed to treat individual infections or infection sites when there was overlap between episodes. Similarly, when patients were kept in hospital because of an infection it was not always possible to attribute responsibility to a single infection episode. Consequently patients with at least one infection during the duration of the study were separated into those who had an ESI (either alone or with infection at other sites) and those who had infection at other sites but never had an ESI.

The distribution of antibiotic costs was highly skewed. Moreover, there was a systematic difference between countries. The cost per patient treated for the 63 patients who received antibiotics in U.K. centres was significantly lower than the costs per patient treated for the 50 patients who received antibiotics in French or Belgian centres. The median difference in antibiotic costs was £45 lower per patient in the U.K. centres (95% CI from £12 to £88 lower; P = 0.01, Mann-Whitney test); the mean difference in antibiotic costs was £283 lower in the U.K. centres (95% CI –£34 to +£601).

There was a marked trend towards lower antibiotic costs per patient treated in the mupirocin group (Table II). Mupirocin treatment was associated with significantly reduced antibiotic costs in the patients with ESI. However, this was offset by a trend towards higher antibiotic costs for patients in the mupirocin group with other infections without ESI, consequently the overall difference in antibiotic costs was not statistically significant (Table II). Overall 69 patients required additional hospitalization

Cost of infection management

Cost of screening and mupirocin prophylaxis. Screening required three nasal swabs, at an estimated cost of £15 per patient. One year of treatment with mupirocin cost £93. The total cost of screening for nasal carriage was £17,160 (£15 × 1144), therefore the cost per identified carrier of S. aureus was £64 (£17,160/267). The combined cost of screening and 1 year of mupirocin prophylaxis was therefore £157 (£93 + £64) for each identified nasal carrier of S. aureus.

Cost of infection management
due to infection, 35 in the mupirocin treatment group and
34 in the placebo treatment group. The duration of
additional hospitalization was lower in the mupirocin
group, particularly for those patients with ESI (Table III).

In the mupirocin group catheter removal was required
for two of 26 (7.7%) patients with ESI compared with four
of 25 (16.0%) patients in the placebo group (odds ratio for
catheter removal 0.44; 95% CI 0.07–2.63). For other
infections without ESI, catheter removal was required for
six (19.4%) of the 31 patients in the mupirocin group and
five (16.1%) of the 31 in the placebo group (odds ratio for
catheter removal 1.35; 95% CI 0.34–4.61).

In summary, there was a trend towards lower healthcare
costs in patients in the mupirocin group who had ESI. This
trend occurred in all three of the independent measures of
healthcare costs used (antibiotic costs, duration of addi-
tional hospital stay and probability of catheter removal),
was statistically significant for antibiotic costs (P = 0.02),
and nearly so for duration of hospitalization (P = 0.065).
In contrast, healthcare costs for patients with other in-
fec tions but no ESI were similar in the mupirocin and placebo
groups, although there was a trend towards higher costs in
the mupirocin group.

A analysis of sensitivity of conclusions on costing to
changes in healthcare costs and rates of exit site
infection

After stratification of patients by country the trend
towards lower costs for patients with ESI who received
mupirocin remained significant for antibiotics (P = 0.02
(Cochran-Mantel-Haenszel test)) and was nearly signifi-
cant for additional hospitalization (P = 0.06). However,
these cost savings were lower than the cost of screening
and mupirocin prophylaxis resulting in total costs
(including mupirocin prophylaxis) being significantly
higher in the mupirocin group (P = 0.001).

The effect of ESI rate was simulated over a range from
20% to 100% with 50 sets of data for each run. For ESI
rates of <75% the total cost of infection management
(including mupirocin prophylaxis) was significantly higher
in the mupirocin group in all simulations. At ESI rates of
>75% there was no significant difference in the costs of
infection management for 23% of simulations and at ESI
rates of >80% there was no significant difference in at
least 50% of simulations. However, the cost of infection
management was never significantly lower in the
mupirocin group.

Table I. Number (%) of patients with infection, the number of infection episodes per patient and the
number of days with infection by treatment group

<table>
<thead>
<tr>
<th>Infections per patient</th>
<th>Mupirocin (%)</th>
<th>Placebo (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESI only</td>
<td>1</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2–5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6–10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>11 (8%)</td>
<td>8 (6%)</td>
<td>19 (7%)</td>
</tr>
<tr>
<td>ESI with other</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2–5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>6–10</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>15 (11%)</td>
<td>17 (13%)</td>
<td>32 (12%)</td>
</tr>
<tr>
<td>Other, excluding ESI</td>
<td>1</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>2–5</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>6–10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>31 (23%)</td>
<td>31 (23%)</td>
<td>62 (23%)</td>
</tr>
<tr>
<td>Patients with no infection</td>
<td>77 (58%)</td>
<td>77 (58%)</td>
<td>154 (58%)</td>
</tr>
<tr>
<td>Total patients</td>
<td>134</td>
<td>133</td>
<td>267</td>
</tr>
<tr>
<td>Total no. of infections</td>
<td>107</td>
<td>123</td>
<td>230</td>
</tr>
<tr>
<td>Days with infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESI s</td>
<td>510</td>
<td>1341</td>
<td>1851</td>
</tr>
<tr>
<td>tunnel infection</td>
<td>192</td>
<td>217</td>
<td>409</td>
</tr>
<tr>
<td>peritonitis</td>
<td>641</td>
<td>847</td>
<td>1488</td>
</tr>
</tbody>
</table>

Table I.
The effect of changing healthcare costs was simulated up to a 100% increase in the costs of hospitalization or antibiotics. If the healthcare costs were increased by 40% then there was no significant difference between mupirocin and placebo in 45% of simulations. However, the cost of infection management was never significantly lower in the mupirocin group, even if healthcare costs were increased by 100%.

Incremental cost-effectiveness over a range of costs for screening and mupirocin prophylaxis

Mupirocin prophylaxis reduced the rate of staphylococcal ESI from one in 28.1 months to one in 99.3 months, or from 0.43 infections to 0.12 per year. The cost of screening plus prophylaxis for 1 year was £157; therefore the cost per staphylococcal ESI avoided was £506 (£157/(0.43 – 0.12)) without consideration of any savings arising from reduction in the cost of infection management. Inclusion of savings from reductions in therapeutic antibiotics reduced the cost per staphylococcal ESI prevented to £262, and this was reduced further to £187 by inclusion of savings from hospitalization avoided. The cost-effectiveness of mupirocin was sensitive to the costs of screening and of mupirocin (Figure). A reduction in the cost of screening by £5 (e.g. from £15 per patient to £10 per patient) reduced the cost per staphylococcal ESI prevented by £22. At a screening cost of £15 per patient, the break-even cost for mupirocin treatment was £40 per patient year with hospitalization costs included, and £19 with hospitalization costs excluded (Figure).
Discussion

Mupirocin significantly reduced the risk of ESIs caused by S. aureus from 0.44 to 0.16 per patient year and this effect was independent of other risk factors. Mupirocin did not reduce the proportion of patients who suffered at least one ESI, but this is to be expected. Measurement of the effects of a strategy aimed at reducing recurrent events should be based on reduction in risk per patient year, not the number of patients with one or more events.

In conducting economic analysis alongside clinical trials a balance must be struck between collection of additional data and the effects which this might have on patient recruitment. The primary aim of most trials is to establish the effectiveness of an intervention and it could be argued that, until this is done, there is little point in collecting data about cost-effectiveness. However, it is usually possible to identify a limited set of cost data which are both easy to measure and important to decision makers. An important first step is to determine whether or not the intervention is likely to be cost-saving. If so there is little point in overburdening clinical trials with additional information that is unlikely to influence decision makers.

Our analysis of costs was restricted to short-term hospital costs which were both measurable within the study protocol and which applied in all of the study centres. These were antibiotics, additional days in hospital and replacement of intraperitoneal catheters. Our pilot survey of the study centres suggested that other procedures, such as therapeutic drug monitoring, dressings and barrier nursing, played a limited role in the management of these infections and that there was marked variation between centres in their application.

Mupirocin reduced the cost of management of patients with exit site infection, because of lower antibiotic costs (Table II) and reduced additional hospitalization in patients who received antibiotic treatment for ESI (Table III). However, the reduction in hospital costs achieved by

Table III. Number of patients who required additional hospitalization for the management of infection with the mean and median length of stay, the differences between medians and means and their 95% confidence intervals (CI)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Mupirocin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESI (alone or with other infections)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no. of patients</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>length of stay (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>19.0</td>
<td>36.5</td>
</tr>
<tr>
<td>mean</td>
<td>25.9</td>
<td>77.6</td>
</tr>
<tr>
<td>difference between medians</td>
<td>-21.0 days (-69.0 to +2.0 days)</td>
<td></td>
</tr>
<tr>
<td>difference between means</td>
<td>-52.1 days (-112.3 to +9.0 days)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>Other infections (excluding ESI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no. of patients</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>length of stay (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>23.0</td>
<td>12.0</td>
</tr>
<tr>
<td>mean</td>
<td>32.9</td>
<td>21.6</td>
</tr>
<tr>
<td>difference between medians</td>
<td>+5.0 days (-3.0 to +18.0 days)</td>
<td></td>
</tr>
<tr>
<td>difference between means</td>
<td>+11.3 days (-5.1 to +27.7 days)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>All infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no. of patients</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>length of stay (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>23.0</td>
<td>22.0</td>
</tr>
<tr>
<td>mean</td>
<td>30.9</td>
<td>44.7</td>
</tr>
<tr>
<td>difference between medians (days)</td>
<td>-1.5 (-10.0 to +7.0 days)</td>
<td></td>
</tr>
<tr>
<td>difference between means (days)</td>
<td>-13.8 (-40.7 to +13.0 days)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

aMann–Whitney test.
Cost-effectiveness of mupirocin prophylaxis in CA PD

Figure. Two way sensitivity analysis of cost per staphylococcal exit site infection (ESI) avoided by cost of mupirocin treatment and by cost of screening for nasal carriage of S. aureus. The unbroken line indicates the cost of screening assumed in the trial analysis. The point at which any line intersects with the x axis indicates the conditions under which mupirocin becomes cost neutral. Cost of screening for nasal carriage of Staphylococcus aureus: ×, £20; ●, £15; ○, £10; ■, £5.

mupirocin is unlikely to offset the cost of mupirocin itself, even if the cost of hospitalization is included. The study was too small to provide conclusive evidence about the effect of mupirocin prophylaxis on rates of catheter loss and peritonitis caused by S. aureus but a long-term, observational study suggests that mupirocin reduces the risk of both these complications.5

Concern has been expressed about the emergence of mupirocin-resistant bacteria.11–13 Mupirocin is not related to other antibacterial drugs, so this problem would not have implications for treatment of infection. However, mupirocin is a vital component of programmes for the control of infection caused by methicillin-resistant strains of S. aureus. The current study did not show any evidence of an increase in either low-level (MIC > 8 mg/L) or high level (MIC > 256 mg/L) resistance to mupirocin in S. aureus despite 1236 patient months of mupirocin exposure.6 In the mupirocin group it appeared that reduction in ESI caused by S. aureus was partially balanced by an increase in ESIs caused by Gram-negative bacteria. These results are similar to those reported in a comparison of long-term mupirocin prophylaxis of CA PD patients in comparison with historical controls5 in whom reduction in the risk of S. aureus infection was also associated with an increase in the number of Gram-negative infections.

In conclusion, mupirocin reduced the risk of ESIs caused by S. aureus but short-term savings in healthcare costs are unlikely to be sufficiently great to offset the cost of mupirocin. Ideally, further randomized controlled trials should be performed which either provide more comprehensive data about the effect of mupirocin on short-term costs, including patients’ quality of life, or are sufficiently large and long-term to measure effects on the rate and consequences of peritonitis caused by S. aureus. In the absence of this information, the decision about whether or not to implement mupirocin should depend on a local analysis of the risk and consequences of infection caused by S. aureus, and consideration of the need to conduct surveillance for infections caused by mupirocin-resistant bacteria.

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References


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