Antimicrobial lock therapy for catheter-related bacteraemia among patients on maintenance haemodialysis

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Sir,

In reference to the review on use of antibiotic locks to treat colonized central venous catheters by Berrington & Gould,1 we report the results of antibiotic lock therapy (ALT) in our haemodialysis unit. Although this technique was first used more than a decade ago, optimal dose, duration and choice of the agent are still not clear. Reports of the efficacy of ALT in oncology settings, parenteral therapy units and haemodialysis patients have been promising.2–4

Patients on maintenance haemodialysis with permanent tunnelled central lines who had at least two documented episodes of catheter-related sepsis with the same organism cultured from blood, and in whom creation of alternative venous access was not feasible, were considered for ALT. Patients were given systemic antibiotics at the beginning of a dialysis session. The solution was allowed to dwell for 48 h in the catheter lumen. Vancomycin 100 mg/L, gentamicin 20 mg/L or amphotericin B 2.5 mg/mL was co-administered with heparin (5000 U/mL) saline in an appropriate volume. This dose was chosen to minimize formation of intraluminal precipitates of heparin with antibiotic. These precipitates are potentially hazardous, but do not significantly reduce the antimicrobial efficacy or anticoagulant activity.5,6

At the end of dialysis, the lumen of the line was filled with a ‘locking volume’ of an antibiotic–heparin saline flush solution. The solution was allowed to dwell for 48–72 h in the catheter lumen while not in use, and withdrawn prior to the next dialysis session. A course of ALT usually involved five consecutive dialysis sessions. Vancomycin 100 mg/L, gentamicin 20 mg/L or amphotericin B 2.5 mg/mL was co-administered with heparin (5000 U/mL) saline in an appropriate volume. This dose was chosen to minimize formation of intraluminal precipitates of heparin with antibiotic. These precipitates are potentially hazardous, but do not significantly reduce the antimicrobial efficacy or anticoagulant activity.5,6

Patients were followed up for clinical evidence of possible line infection while the treated catheter remained in situ for up to 3 months. Central and peripheral blood cultures were taken if the patient developed signs of sepsis and differential time to positivity in a continuously monitored blood culture system to identify infections of line origin.7 In addition, blood cultures were taken weekly from the central line at the end of dialysis, up to 4 weeks after cessation of intraluminal therapy.

Study endpoints were: clinical improvement on treatment, microbiological clearance on treatment, clinical and/or microbiological relapse on follow-up, line removal due to sepsis and death due to line-related infection. Clinical outcome measures were defined as follows. Partial response: resolution of symptoms while on ALT followed by clinical relapse within 2 weeks of the end of ALT. Complete response (short term): symptoms resolve and patient remains well 4 weeks post-ALT. Complete response (long term): symptoms resolve during therapy and patient remains well 12 weeks post-ALT.

From May to November 2000, we followed up eight patients on maintenance haemodialysis with 10 episodes of catheter-related sepsis, who were administered ALT (Table 1). These patients had at least two documented episodes of sepsis with the same organism, and were given systemic vancomycin and/or gentamicin depending on the blood culture results. The most common organisms isolated were coagulase-negative staphylococci (n = 3). Patient 1 was non-evaluable as she had less than three doses of ALT before she died. Initial clinical improvement was seen in five of seven evaluable patients (71%) and seven of nine episodes. Immediate post-ALT cultures were negative in six of nine episodes, but later relapse with a similar organism occurred in two of these patients (patient 2, positive central line tip culture and clinical features of infection; patient 7, relapsed with Citrobacter after a second course of ALT). Therefore, microbiological evidence of continuing infection was seen in four of seven patients (57%). Further genotyping of these isolates to confirm microbiological failure rather than reinfection was not performed. Infection forced catheter removal in these four patients. Overall, partial response was seen in five of nine (56%) episodes, short-term complete response in one of nine (11%) episodes and long-term complete response in three (33%) episodes.

Not surprisingly, the outcome was better in patients infected with less virulent organisms (i.e. coagulase-negative staphylococci and enterococci) than with Gram-negative organisms or yeast. Although similar numbers of Gram-positive and -negative infections were observed, complete response after ALT was observed in all three patients with Gram-positive infections and only one patient with Gram-negative bacteraemia. Catheter-related sepsis due to Candida (patient 7) did not respond to amphotericin line lock. Prolongation of catheter survival by >3 months was achieved in...
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Table 1. Results of monitoring patients on antibiotic locking therapy for catheter-related infection

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Culture pre-treatment</th>
<th>ALT antibiotic used</th>
<th>Culture at end of ALT treatment</th>
<th>Catheter removal</th>
<th>Reason for removal</th>
<th>Prolongation of catheter survival/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Enterococcus,</em> EMRSA 16</td>
<td>vancomycin</td>
<td><em>Enterococcus</em></td>
<td>–</td>
<td>–</td>
<td>non-evaluable (patient expired)</td>
</tr>
<tr>
<td>2</td>
<td><em>Escherichia coli,</em> Klebsiella</td>
<td>gentamicin</td>
<td>no growth</td>
<td>yes</td>
<td>infection</td>
<td>45 days/partial response</td>
</tr>
<tr>
<td>3</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>gentamicin</td>
<td><em>P. aeruginosa</em></td>
<td>yes</td>
<td>infection</td>
<td>23 days/partial response</td>
</tr>
<tr>
<td>4</td>
<td><em>Enterococcus</em></td>
<td>vancomycin</td>
<td>no growth</td>
<td>no</td>
<td>–</td>
<td>&gt;3 months/complete response, long term</td>
</tr>
<tr>
<td>5</td>
<td>CNS</td>
<td>vancomycin</td>
<td>no growth</td>
<td>no</td>
<td>–</td>
<td>&gt;3 months/complete response, long term</td>
</tr>
<tr>
<td>6</td>
<td>CNS</td>
<td>vancomycin</td>
<td>no growth</td>
<td>no</td>
<td>–</td>
<td>51 days/complete response, short term</td>
</tr>
<tr>
<td>7</td>
<td><em>Acinetobacter baumannii,</em> CNS</td>
<td>gentamicin</td>
<td><em>P. aeruginosa</em></td>
<td>yes</td>
<td>infection, blocked</td>
<td>34 days/partial response, re-infection</td>
</tr>
<tr>
<td>8</td>
<td><em>Citrobacter</em></td>
<td>gentamicin</td>
<td>no growth</td>
<td>no</td>
<td>–</td>
<td>21 days/partial response</td>
</tr>
<tr>
<td>9</td>
<td><em>Candida parapsilosis</em></td>
<td>gentamicin</td>
<td><em>C. parapsilosis,</em> <em>Citrobacter</em></td>
<td>yes</td>
<td>infection</td>
<td>28 days/partial response</td>
</tr>
</tbody>
</table>

CNS, coagulase-negative staphylococci.

three of nine (33%) episodes and >1 month in six of nine (66.7%) episodes.

To conclude, ALT is a simple, economical, safe and easily administered therapy for catheter-related bacteraemia. It achieves higher concentrations of antibiotic within the lumen and avoids potential toxicity of systemic antibiotics. The catheter salvage rate achieved in this study was low compared with previous studies in oncology, haemodialysis and parenteral nutrition units. This may reflect the lower dose of antimicrobials used and also the similar numbers of Gram-positive and negative infections in our patients, compared with a predominance of Gram-positive infections in other reports.2,3 Furthermore, these patients had already failed systemic therapy. However, even short-term prolongation of catheter placement can be of considerable clinical benefit in haemodialysis patients with few remaining options for vascular access.

The data presented here should not be regarded as evidence of ALT and single dose systemic therapy being more effective than standard systemic antimicrobials as initial treatment for catheter-related sepsis. Exploring this possibility would require a randomized trial.

The concentration of heparin used in catheter flush solutions varies between haemodialysis units; some question the role of heparin in reducing the risk of central venous catheter thrombosis.8 Lowering the dose of heparin in our locking solution may enable safe administration of a higher dose of antibiotic. There was no evidence of any adverse consequence due to antibiotic–heparin particulates, and the risk of these in this context remains theoretical. Longer duration of ALT, higher dose of antibiotic (especially for Gram-negative organisms) and daily dosing may further reduce treatment failure in these patients.

References

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