The clinical efficacy of continuous-infusion flucloxacillin in serious staphylococcal sepsis

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Since the efficacy of \(\beta\)-lactams against pathogens such as methicillin-susceptible \textit{Staphylococcus aureus} (MSSA) is related to the time for which serum drug concentrations exceed the MIC for the pathogen, administration of anti-staphylococcal \(\beta\)-lactams by continuous infusion may provide a more suitable means of drug delivery than intermittent dosing. To assess the clinical efficacy of continuous-infusion therapy, we reviewed the outcomes for 20 consecutive patients with proven serious MSSA sepsis (three with endocarditis, ten osteomyelitis, one endocarditis plus osteomyelitis and six deep abscess) treated with continuous-infusion flucloxacillin (8–12 g/day). Patients initially receiving routine intermittent-dose flucloxacillin therapy were changed to continuous-infusion flucloxacillin (mean duration 29 days; range 4–60 days) for completion of their treatment course. In the majority of cases this was given at home. Serum flucloxacillin concentrations during continuous-infusion flucloxacillin 12 g/day were 11.5–40 mg/L (ten patients) and those during continuous-infusion flucloxacillin 8 g/day were 8–40 mg/L (five patients), these concentrations being well above the expected MIC of flucloxacillin for MSSA. Continuous-infusion flucloxacillin was well tolerated by most patients, and 14/17 patients (82%) who completed their course of continuous-infusion flucloxacillin were judged clinically and microbiologically cured at long-term follow-up (mean 67 weeks; range 4–152 weeks). These preliminary data suggest that, following initial intermittent-dose flucloxacillin therapy, continuous-infusion flucloxacillin is an effective treatment option for serious MSSA sepsis, and forms a feasible and possibly preferable alternative to glycopeptides when considering home-based parenteral therapy for these infections. Further studies are needed to identify whether continuous-infusion flucloxacillin can entirely replace intermittent-dose therapy for such infections.

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Patients and methods

Since August 1993, all patients at Monash Medical Centre with proven MSSA sepsis who were considered suitable for home-based iv care via the ‘Hospital-in-the-Home’ (HITH) unit were considered for continuous-infusion flucloxacillin therapy. Patients needed to be clinically stable, have long-term iv access established and have suitable home social support. Exclusion criteria included β-lactam allergy, unstable clinical disease or insufficient social support for home care. In some cases, patients were initially considered suitable for home therapy and continuous-infusion flucloxacillin therapy was commenced, but later their clinical state changed such that they ultimately remained inpatients throughout their care. Data regarding these patients have, never the less, been included, since they received continuous-infusion flucloxacillin.

All patients received intermittent flucloxacillin therapy initially, and had venous access established either via a peripherally-inserted central catheter (PICC) or a Hickman catheter (Table). At the discretion of the physicians initially treating the patients, intermittent flucloxacillin therapy was administered as a total dose of 8 g/day (2 g every 6 h) or 12 g/day (2 g every 4 h). If clinically improving, patients were continued on the same total daily dose when changed to continuous-infusion flucloxacillin. Subsequent dosage alterations were based either on the patients’ symptoms (for example, nausea associated with 12 g/day led to a dose reduction to 8 g/day) or on serum concentrations.

S. aureus isolates were identified by routine methods and susceptibility to oxacillin was detected by disc sensitivity testing according to NCCLS guidelines. Oxacillin MICs for selected isolates were measured using E test (AB Biodisk, Solna, Sweden).

Solutions containing either 8 or 12 g flucloxacillin sodium (CSL, Victoria, Australia) were prepared by the Monash Medical Centre Pharmacy Department in 120 mL of sterile water three times weekly and were stored in patients’ home refrigerators at 4°C until needed for daily use. Using this protocol, there is no substantial loss of flucloxacillin potency after 24 h at room temperature (25°C) or after 72 h at 5°C. The flucloxacillin was delivered via a portable battery-operated Abbott Provider 5500 Pump (Abbott Laboratories, Chicago, IL, USA). Patients managed at home were seen by an HITH nurse daily, reviewed by a medical officer at least weekly and had haematological and biochemical parameters monitored once per week.

Serum specimens for measurement of flucloxacillin concentrations were obtained from peripheral venepuncture once steady state had been reached and were analysed immediately or stored at −80°C for later assessment. Flucloxacillin concentrations were measured by standard bioassay on Mueller–Hinton agar with S. aureus ATCC 25923 as the test organism and pooled fresh frozen human plasma as the diluent for the controls. Standard solutions and patient specimens were both measured in duplicate.

The upper limit of this assay was flucloxacillin 40 mg/L. For comparison with the concentrations identified by bioassay, selected patients also had serum flucloxacillin concentrations measured by high-pressure liquid chromatography (HPLC) with detection by UV absorption at 230 nm.

The case records of all patients treated with continuous-infusion flucloxacillin were reviewed to determine patient demographics, underlying medical condition, indication for antibiotic therapy, duration and dosage of intermittent-dose and continuous-infusion therapy, method(s) of iv access, laboratory results, side effects, and clinical and microbiological outcome.

Results

Twenty patients with proven MSSA infection received continuous-infusion flucloxacillin during the 4 year period of this review. Patients were typical of those commonly encountered with serious MSSA sepsis. Their mean age was 40.6 years (range 16–69 years) and there were 15 males and five females. Diagnoses included endocarditis (n = 3), osteomyelitis (n = 10), endocarditis plus osteomyelitis (n = 1) and deep abscess (n = 6). Predisposing factors for MSSA infection were noted in 17 of the 20 patients (Table). All S. aureus isolates were susceptible to oxacillin as judged by disc sensitivity testing, and oxacillin MICs for selected isolates (cases 2-6) were 0.25–0.5 mg/L.

Before commencing continuous-infusion flucloxacillin, all patients initially received routine intermittent-dose flucloxacillin therapy for a mean of 20 days (range 5–56 days) (Table). The mean duration of continuous-infusion flucloxacillin was 29 days (median 33 days; range 4–60 days). Fifteen patients initially received 12 g/day, and five initially received 8 g/day. Seventeen patients were treated with flucloxacillin alone and three patients (cases 1, 3 and 4) received concurrent adjunctive oral rifampicin due to perceived slow initial clinical progress with intermittent-dose flucloxacillin. Twelve patients required surgery or a drainage procedure in addition to antibiotic therapy.

Serum flucloxacillin concentrations, which were assessed in 13 of the 17 patients receiving flucloxacillin alone, were measured 3–15 days after commencing continuous-infusion flucloxacillin (mean 7.7 days). Patients receiving 8 g/day had serum concentrations of 8–40 mg/L (median 29 mg/L) and those on 12 g/day flucloxacillin had serum concentrations of 11.5–40 mg/L (median 27 mg/L) as judged by bioassay. For five patients the flucloxacillin levels were also measured by HPLC, the results of which correlated well with the results of bioassay (Table). Two patients (cases 10 and 14) who initially received 8 g/day flucloxacillin had their doses increased to 12 g/day due to perceived low flucloxacillin levels (both 8 mg/L). One patient (case 3) who was initially on 12 g/day had the dose reduced to 8 g/day because of possible flucloxacillin-associated nausea.
# Table. Clinical details of patients who received continuous infusion flucloxacillin

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Predisposing factors</th>
<th>Diagnosis</th>
<th>Length of therapy (days)</th>
<th>Serum flucloxacillin (mg/L) determined by</th>
<th>Adjunctive therapy</th>
<th>Subsequent oral antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>iv drug use, pacemaker insertion</td>
<td>endocarditis/abscesses</td>
<td>intermittent 40, cont. infusion 17</td>
<td>unreliable, HPLC 12</td>
<td>PICC</td>
<td>rifampicin</td>
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<td>pacemaker pocket infection</td>
<td>endocarditis/abscesses</td>
<td>6, 37</td>
<td>12</td>
<td>PICC</td>
<td>pacemaker</td>
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<tr>
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<td>64</td>
<td>rheumatic fever/bicuspid aortic valve</td>
<td>endocarditis/abscesses</td>
<td>51, 39</td>
<td>12 g (7 days), 8 g (32 days)</td>
<td>unreliable, HPLC Hickman</td>
<td>Hickman infection</td>
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<td>25</td>
<td>chronic granulomatous disease</td>
<td>hepatic abscesses</td>
<td>53, 21</td>
<td>12</td>
<td>PICC</td>
<td>relapse at 8 months</td>
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<td>5</td>
<td>16</td>
<td>steroids</td>
<td>psoas abscesses</td>
<td>10, 32</td>
<td>8</td>
<td>PICC</td>
<td>–</td>
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<tr>
<td>6</td>
<td>45</td>
<td>–</td>
<td>osteomyelitis</td>
<td>6, 36</td>
<td>12</td>
<td>PICC</td>
<td>–</td>
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<tr>
<td>7</td>
<td>60</td>
<td>recent surgery: laminectomy</td>
<td>osteomyelitis</td>
<td>21, 9</td>
<td>12</td>
<td>ND, Hickman</td>
<td>rash</td>
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<tr>
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<td>61</td>
<td>recent surgery: cardiac bypass</td>
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<td>29, 16</td>
<td>12</td>
<td>ND</td>
<td>PICC</td>
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<td>9</td>
<td>69</td>
<td>diabetes</td>
<td>deep abscess</td>
<td>13, 29</td>
<td>12</td>
<td>&gt;40</td>
<td>PICC then Hickman</td>
</tr>
<tr>
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<td>osteomyelitis</td>
<td>11, 50</td>
<td>8 g (7 days), 12 g (43 days)</td>
<td>8 g:8 then 12 g:31</td>
<td>PICC then Hickman</td>
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<tr>
<td>11</td>
<td>32</td>
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<td>deep abscess</td>
<td>22, 4</td>
<td>12</td>
<td>ND</td>
<td>Hickman</td>
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<tr>
<td>12</td>
<td>60</td>
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<td>56, 16</td>
<td>8</td>
<td>&gt;40</td>
<td>PICC then Hickman</td>
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<td>59</td>
<td>recent repair of Achilles tendon</td>
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<td>5, 24</td>
<td>8</td>
<td>&gt;40</td>
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<tr>
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<td>23</td>
<td>–</td>
<td>osteomyelitis</td>
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<td>8 g (19 days), 12 g (16 days)</td>
<td>8 g:8 then 12 g:19</td>
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<tr>
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<td>23</td>
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<td>10, 34</td>
<td>12</td>
<td>33</td>
<td>PICC</td>
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<tr>
<td>17</td>
<td>43</td>
<td>recent surgery excision of soft tissue cyst</td>
<td>osteomyelitis</td>
<td>9, 42</td>
<td>12</td>
<td>24</td>
<td>PICC</td>
</tr>
<tr>
<td>18</td>
<td>17</td>
<td>rheumatic fever/mitral valve repair</td>
<td>endocarditis</td>
<td>16, 9</td>
<td>12</td>
<td>ND</td>
<td>PICC</td>
</tr>
<tr>
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<td>47</td>
<td>osteomyelitis</td>
<td>osteomyelitis</td>
<td>14, 39</td>
<td>12</td>
<td>&gt;40</td>
<td>PICC</td>
</tr>
<tr>
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<td>27</td>
<td>Exciting sarcoma</td>
<td>osteomyelitis</td>
<td>6, 60</td>
<td>12</td>
<td>29</td>
<td>PICC</td>
</tr>
</tbody>
</table>

ND, not done; PICC, peripherally inserted central catheter.
Seventeen patients completed their expected course of continuous-infusion flucloxacillin therapy. Of the remaining three patients, two ceased early as a result of the development of a presumed flucloxacillin-associated rash (cases 7 and 11), while another patient (case 18) was readmitted because of social difficulties unrelated to her antibiotic therapy and completed her flucloxacillin course by intermittent-dose therapy as an inpatient. Thus, of the 17 patients who were clinically assessable after continuous-infusion flucloxacillin, all were clinically and bacteriologically cured at the end of therapy.

Subsequent to continuous-infusion flucloxacillin therapy, nine patients received no further antibiotic therapy, while eight patients received ongoing treatment with oral flucloxacillin for various durations (Table). The reasons for ongoing oral therapy included the presence of immunsuppression (case 4), complex surgical interventions (cases 8 and 10) or chronic osteomyelitis (cases 16, 17 and 19).

Prolonged follow-up after continuous-infusion flucloxacillin therapy (mean 67 weeks, range 4–152 weeks) was achieved in the majority of patients. Fourteen of the 17 patients who completed their continuous-infusion flucloxacillin course remained well at follow-up, but three patients who initially responded to continuous-infusion flucloxacillin subsequently relapsed, despite ongoing oral therapy. One patient (case 4) who had chronic granulomatous disease resulting in recurrent staphylococcal infections represented with a MSSA liver abscess 11 months after ceasing continuous-infusion flucloxacillin. Another patient (case 8) with sternal osteomyelitis and mediastinitis following coronary artery bypass surgery was managed with iv then oral flucloxacillin, but nine weeks after ceasing all antibiotic therapy was again found to have MSSA in the sternal wound. The third patient (case 10), who had MSSA osteomyelitis related to a metal fixation device for a compound fracture of the ulna, was also treated with iv then oral flucloxacillin, but relapsed after 1 month of oral therapy.

No significant haematological and biochemical complications were noted; in particular, no patients developed flucloxacillin-associated neutropenia or hepatitis. Intravenous catheter exit site infections with Escherichia coli (case 19) Enterobacter cloacae (case 14) and Klebsiella pneumoniae (case 3) were noted in three patients receiving continuous-infusion flucloxacillin. All cases resolved with either simple removal of the venous access device alone (in one patient) or a combination of device removal and a brief course of oral ciprofloxacin (in the other two patients).

Overall, a total of 554 days of treatment were administered at home. Aiter allowing for occasional brief readmissions for reseating of iv access, a total of 545 inpatient days were saved (mean 27.3 per patient).

Discussion

Despite pharmacodynamic, in-vitro and animal data in favour of administering β-lactam antibiotics via continuous infusion, there have been few reported human clinical trials examining the efficacy of this mode of antibiotic administration. The aim of this study, therefore, was to examine the efficacy and tolerance of continuous-infusion flucloxacillin in patients with serious staphylococcal sepsis and to explore a potential drug delivery model that was suitable for home-based care.

In-vitro and animal studies suggest that the best predictor of bacterial killing by β-lactams in vivo is the time for which drug concentrations in serum/tissue exceed the MIC for the pathogen, rather than other parameters such as peak concentration or area under the time-concentration-distribution curve of drug exposure. Compared with intermittent dosing, β-lactam tissue penetration appears to be at least similar, and possibly improved, with continuous-infusion administration. In addition, animal studies show no evidence of any undesirable effects associated with continuous infusion of β-lactams. No deleterious impact has been observed in the development of drug resistance and few concentration-dependent side effects have been noted. Aecdotal reports have suggested clinical success with continuous-infusion β-lactam therapy in some neutropenic patients with severe recalcitrant Gram-negative infections. However, to our knowledge, there are no published data regarding the efficacy of continuous-infusion therapy for severe staphylococcal infections.

S. aureus bacteraemia has an overall mortality of 20–30% and diseases such as S. aureus endocarditis are associated with a mortality of 20–70%. Since the first week of disease is generally associated with the highest rates of mortality, routine therapy with 8–12 g/day intermittent-dose flucloxacillin was administered until the source of infection was identified and the patient stabilized. In appropriate patients (see Patients and methods), the regimen was then changed to continuous-infusion flucloxacillin. Thus, although our study assessed consecutive cases, patients selected as being suitable for continuous-infusion flucloxacillin may have been more likely to achieve a satisfactory clinical and microbiological outcome than a random sample of patients with staphylococcal bacteraemia. Under these circumstances, we found continuous-infusion flucloxacillin to be associated with at least an 82% rate of clinical and microbiological cure (14 of 17 patients who completed therapy). Among the three cases who ‘failed’ continuous-infusion flucloxacillin, two had clinical features that made long-term cure unlikely, while in the third case it was unclear whether the patient had ongoing MSSA infection or simply wound colonization.
Continuous-infusion flucloxacillin

The optimal dose of flucloxacillin for continuous infusion is uncertain at present. The routine flucloxacillin dose for serious staphylococcal infections at our institution is 2 g iv every 4–6 h (8–12 g/day), hence we administered the same total daily dose by continuous infusion. Nevertheless, pharmacokinetic studies suggest that a smaller total daily dose delivered by continuous infusion may produce serum concentrations similar to those achieved with intermittent dosing. Since oxacillin sodium and nafcillin sodium are similar in their pharmacological stability to flucloxacillin after reconstitution, these agents may also be possible candidates for administration by continuous infusion although efficacy and toxicity data under these circumstances are currently lacking.

We used a standard bioassay technique to measure serum flucloxacillin concentrations. Patients receiving flucloxacillin 12 g/day had serum concentrations of 11.5–40 mg/L (median 27 mg/L); these were similar to those reported by Visser et al. Patients receiving 8 g/day had concentrations of 8–40 mg/L (median 29 mg/L). These concentrations are likely to be 16–80 times the maximum expected MIC of flucloxacillin for the infecting isolates (0.5 mg/L), but it is uncertain how they compare with expected serum levels following similar dose intermittent flucloxacillin therapy.

Craig & Ibert and Leggett et al. have suggested that, for highly protein-bound drugs, such as flucloxacillin, the accurate measurement of serum concentrations of free, active drug requires the ultrafiltration of serum prior to bioassay. Although such ultrafiltration was not undertaken in this study, a crude estimate of the expected level of free flucloxacillin activity can be calculated by assuming that our patients had normal levels of protein binding (93%) for flucloxacillin and that the MIC of flucloxacillin for each S. aureus isolate was ≤0.5 mg/L. Under these circumstances, concentrations of free flucloxacillin in those patients receiving 12 g/day were likely to be 1.6–2.8 times the MIC for each infecting strain. These data suggest, therefore, that continuous-infusion flucloxacillin 8–12 g/day achieves serum concentrations that are likely to be active against MSSA, regardless of whether one considers the serum concentrations of total (protein-bound and unbound) or free flucloxacillin.

In general, continuous-infusion flucloxacillin was well tolerated. No serious adverse reactions attributable to continuous-infusion flucloxacillin were noted, other than the development of an allergic rash in two patients and possible dose-related nausea in one patient. Three patients developed minor venous access exit-site infections which resolved with line removal and oral antibiotics. Such complications, despite careful nursing care, reflect the difficulty in maintaining long-term venous access in such patients.

Of the 18 patients who received continuous-infusion flucloxacillin at home, a total of 545 days’ drug delivery was provided via HITH care rather than as inpatients. Other alternatives to flucloxacillin (or other antistaphylococcal penicillins) for home-based treatment of staphylococcal infections include glycopeptides such as vancomycin and teicoplanin. However, in-vitro and in-vivo studies suggest that flucloxacillin treatment results in more rapid bacterial killing of MSSA isolates than vancomycin and it does not generally require monitoring of drug levels. Since the emergence of multi-resistant pathogens such as vancomycin-resistant enterococci and vancomycin-intermediate S. aureus, there may also be advantages in using non-glycopeptide therapy whenever possible. Cost comparisons between continuous-infusion flucloxacillin and glycopeptides for home-based therapy are limited. The cost of home-based vancomycin therapy, including pharmaceutical, nursing, delivery and monitoring costs, for serious staphylococcal disease at our institution is approximately 210 A australian dollars/day. Using similar methodology, we estimate the cost of continuous-infusion flucloxacillin therapy to be 85–100 A australian dollars/day (data not shown).

This study suggests that continuous-infusion flucloxacillin is a safe, effective and convenient therapeutic option for the treatment of patients with serious MSSA sepsis who are clinically stable, and that it may enable some patients to receive their antibiotics via a home-based programme. Although we did not determine the optimal daily dose of flucloxacillin for continuous infusion, 8–12 g/day results in steady-state serum concentrations well above the expected MIC of flucloxacillin for MSSA isolates. Further studies will be necessary to address the role of continuous-infusion flucloxacillin in initial acute therapy of severe staphylococcal infections.

Acknowledgements

The authors would like to thank Dr Phillip Paull and Miss Jackie Williams for their assistance with the serum flucloxacillin measurements, as well as the staff from the HITH Unit.

References

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Received 7 January 1998; returned 6 March 1998; revised 6 April 1998; accepted 23 August 1998

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