posterior presentations in 2003 (Forty-third Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract A-22) and 2004 (Fourteenth European Congress of Clinical Microbiology and Infectious Diseases, Abstract 902) and tigecycline has not been studied for UTI treatment besides case series.3

A follow-up letter suggested that use of a higher than recommended dose may be effective for MDR Klebsiella pneumoniae or Acinetobacter baumannii urosepsis.4 Moreover, the author provided ‘estimates’ of serum and urinary concentrations following 100, 200 and 400 mg loading doses, and 50 mg every 12 h, 100 mg every 12 h and 200 mg every 24 h maintenance doses, respectively.3,4 Urine concentration was assumed to be ∼0.3, 0.6 or 1.2 mg/L depending on the dosing schedule at an unstated time post-dose based on a serum concentration of 1.5, 3.0 or 6.0 mg/L, respectively.4 A linear relationship between dose and plasma/urine concentration was assumed and urine concentrations were calculated to be 20% of serum concentrations. Neither of these claims has a pharmacokinetic basis or considered varying dosing intervals. The assumption of linearity also contradicted a statement made in the letter about tigecycline kinetics resembling doxycycline’s concentration-dependent kinetics at high doses.4

If one accepts that 15%–22% of tigecycline is excreted unchanged in the urine with standard dosing of 50 mg every 12 h, then the amount excreted would be 100 mg/day × 0.15–0.22 (i.e. 15–22 mg/day). Typical urine output is generally <2 L/day; thus, urinary concentrations should average 7.5–11 mg/L or greater.

In a clinical pharmacology review, 14.8% of a 50 mg dose was claimed to be excreted as tigecycline epimer and 2.0% was claimed to be excreted as unchanged drug.5 The tigecycline epimer was described as pharmacologically inactive. However, tracing these data to the original published report revealed that the percentages were reversed.6 Unchanged tigecycline urine excretion of 14.8% rather than 2.0% is consistent with the low-end percentage excreted range reported in the literature. Average tigecycline urine concentrations are expected to exceed the MIC for Gram-negative isolates reported as susceptible by several-fold; however, there is concern over whether serum concentrations would also exceed the MIC in bacteremic patients. Nothing has been published about the activity of tigecycline in urine and the extent that activity depends on urine pH or metal cation concentrations. Tigecycline should not be used for UTI when other therapies including aminoglycosides, carbapenems and colistin are options; however, in rare situations, tigecycline may be considered. Current data do not support the need for or safety of high-dose tigecycline as suggested by Cunha et al.3 and Cunha.6

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Therapeutic serum concentrations of daptomycin after intraperitoneal administration in a patient with peritoneal dialysis-associated peritonitis

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Keywords: pharmacokinetics, PK, cyclic lipopeptides

Sir, Peritonitis remains a leading complication of peritoneal dialysis. It frequently requires hospitalization, and is sometimes associated with death of the patient. Severe and prolonged peritonitis can lead to peritoneal membrane thickening and thereby to failure of this dialysis technique.1 The treatment of peritoneal dialysis-associated peritonitis is becoming increasingly...
challenging owing to the increase in methicillin- and vancomycin-resistant strains. Daptomycin is a new cyclic lipopeptide antibiotic used for the treatment of infections caused by Gram-positive organisms, especially complicated skin and soft tissue infections, right-sided endocarditis and serious life-threatening Gram-positive infections, including those due to both susceptible and resistant strains of Staphylococcus aureus as well as vancomycin-resistant enterococci. Antimicrobial activity of daptomycin against S. aureus isolates for dialysis patients is reported to be 4- to 8-fold more potent than vancomycin and linezolid. Therefore daptomycin seems to be an interesting antibiotic agent to be used in patients on peritoneal dialysis. While there are several publications on the use and dosing of daptomycin in patients with chronic kidney disease as well as in patients with acute kidney injury there are only scarce data on pharmacokinetics and use in patients on peritoneal dialysis. Recently, Goedecke et al. published pharmacokinetic data of daptomycin given intravenously to a patient on peritoneal dialysis yielding therapeutic concentrations of daptomycin in blood and peritoneal fluid. Yet the standard approach to treatment of peritoneal dialysis-associated peritonitis is the intraperitoneal use of antibiotics. Huen et al. were the first to describe two cases of vancomycin-resistant Enterococcus peritonitis successfully treated with intraperitoneal administration of daptomycin. However, it is not known whether intraperitoneal use would be associated with therapeutically relevant blood concentrations of daptomycin. We therefore analysed pharmacokinetic data of daptomycin given intravenously to a patient on peritoneal dialysis for treatment of peritonitis.

A 48-year-old white female had been admitted with abdominal pain and fever up to 38.5°C due to peritonitis. Symptoms occurred a day prior to admission. She had been on peritoneal dialysis due to oxalate nephropathy since 2007. Her past medical history included short bowel syndrome due to mesenteric ischaemia based on protein C and protein S deficiency. She had a permanent central venous catheter device for parenteral nutrition. The venous access had been replaced several times in the past due to colonization with S. aureus. Five weeks prior to admission she was treated with daptomycin intravenously for septicemia caused by a colonized femoral central venous catheter, which subsequently had been explanted. Physical examination showed a malnourished patient with abdominal pain but no muscular defence. The patient was hypotensive (blood pressure 70/55 mmHg), afebrile (temperature 36.8°C) and had a heart rate of 67 beats per min. The peritoneal fluid was cloudy. For several years she had suffered from leucopenia, therefore her white blood cell count was not elevated; interestingly serum inflammation markers were not elevated. We assumed a re-infection with S. aureus without elevation of serum inflammation markers so far. Therefore we decided to administer daptomycin again. An intraperitoneal administration of daptomycin seemed to be more reasonable to treat peritonitis, particularly as no vascular access was available. Informed consent for additional blood samples was obtained from the patient. Daptomycin was given at a dose of 7 mg/kg of body weight intraperitoneally (absolute dose of 280 mg of daptomycin) after the end of automated peritoneal dialysis and remained for 12 h. Blood was taken 15 min, 30 min, 3.5 h and 25 h after injection in order to study pharmacokinetics after intraperitoneal administration. Samples were centrifuged at 2800 g for 5 min at 4°C and stored at −80°C until analysis. Daptomycin concentrations were measured using an HPLC method as previously described.

Our case report provides for the first time data on plasma daptomycin concentrations after intraperitoneal administration of daptomycin. At least in the state of peritonitis the intraperitoneal administration of daptomycin leads to plasma concentrations of daptomycin that are above the MIC for methicillin-resistant S. aureus (‘MRSA’) and vancomycin-resistant enterococci (‘VRE’) (Figure 1). As in the report by Huen et al. intraperitoneal administration of daptomycin was well tolerated and effective. We suggest that it is a reasonable alternative for the treatment of peritonitis. Future studies have to clarify whether the intraperitoneal use of daptomycin might also be suitable to treat systemic Gram-positive infections in peritoneal dialysis patients, especially in patients in which vascular access is difficult to obtain.

An important limitation in prescribing intraperitoneal daptomycin is that it is considered unstable in dextrose solutions. Yet in vitro studies showed a continued bactericidal effect in 2.5% standard dialysate at 37°C up to 24 h. An in vitro experiment using different peritoneal dialysis solutions could not show a significant reduction in daptomycin over a period of 4 h (V. Goedecke, S. M. Bode-Böger, J. T. Kielsstein and M. Hiiss, unpublished results). To avoid accumulation, daptomycin should be given every 48 h, as described for intravenous dosing in peritoneal dialysis patients.

In our opinion, daptomycin can be given intraperitoneally in peritoneal catheter-related infections. Further pharmacokinetic studies are required along with clinical studies to investigate possible untoward effects of intraperitoneal administration of daptomycin.

Figure 1. Plasma concentrations of daptomycin after intraperitoneal administration of a single dose of 7 mg/kg of body weight at the end of cycler-assisted peritoneal dialysis, remaining for 12 h intraperitoneally.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Daptomycin (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>100</td>
</tr>
</tbody>
</table>

**MIC<sub>90</sub> for MRSA**

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Daptomycin in synovial fluid during treatment of methicillin-resistant Staphylococcus aureus septic arthritis

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Keywords: MRSA, osteoarticular infections, cyclic lipopeptide antibiotics

Sir,

Methicillin-resistant Staphylococcus aureus (MRSA) osteoarticular infections present a therapeutic challenge, requiring the adequate removal of infected materials and antibiotic penetration to give therapeutic concentrations at the infection site. Daptomycin, a cyclic lipopeptide antibiotic with a broad spectrum of activity against Gram-positive organisms including MRSA, is an emerging therapy in osteoarticular infection. However, to our knowledge, there are no data on daptomycin osteoarticular tissue penetration.

Herein, we report therapeutic intra-articular concentrations in a case of daptomycin-treated MRSA septic arthritis.

A 41-year-old man with haemoglobin S/C disease (a sickle-cell disorder) and asymptomatic, antiretroviral-therapy-naïve HIV infection presented with a hot, swollen left knee. A long complicated history of recurrent MRSA infection involving his left hip, femur and knee followed an infected total hip replacement 6 years previously. Despite a Girdlestone procedure, extensive chronic osteomyelitis had developed. Prolonged suppressive antibiotic therapy was associated with a 3 year period free of overt infection. Knee aspiration revealed thick pus and MRSA susceptible to vancomycin, teicoplanin, sodium fusidate, tetracyclines, linezolid and daptomycin, but resistant to rifampicin, trimethoprim and clindamycin. The MIC of daptomycin was 0.38 mg/L by Etest. Antibiotic options were limited by previous hepatotoxicity with glycopeptides and peripheral neuropathy with linezolid. Arthroscopic washout of the joint was performed and 6 mg/kg daptomycin was used in combination with 500 mg of oral sodium fusidate 8 hourly. On day 14 of daptomycin therapy, the left knee was aspirated and samples were collected for culture and daptomycin concentration quantification. A simultaneously drawn serum sample was also obtained for daptomycin concentration. Synovial fluid was serosanguineous, not blood stained and culture was negative. Samples for daptomycin assay collected in glass and plastic containers were assayed for the presence of daptomycin, as previously described.1 Daptomycin serum concentration was 12.9 mg/L and synovial fluid concentrations were 9.0 mg/L (glass) and 7.3 mg/L (plastic), suggesting that some daptomycin might have bound to the plastic tube (CLSI susceptibility breakpoint for daptomycin MIC of 1 mg/L). Daptomycin was continued with oral sodium fusidate, with clinical response, and therapy was completed via the outpatient parenteral antibiotic therapy service.

Although unlicensed for osteoarticular infections, daptomycin is increasingly used for this indication, often in combination with other agents. Published case reports, mainly where daptomycin is used second line, suggest cure or improvement in 91% of cases.2 However, judging response to therapy retrospectively is difficult in bone and joint infection, particularly as long-term outcome data are so important. In the only randomized, controlled trial data to date, a subgroup with bone and joint infections was identified in a study of complicated S. aureus bacteraemia.3 Outcomes in this small group of patients were similar between daptomycin monotherapy and standard therapy, with a successful outcome reported in 67% of patients treated with daptomycin compared with 55% of those treated with standard therapy.

To our knowledge, this is the first time that daptomycin concentrations in synovial fluid have been documented. From preclinical data, it is known that daptomycin penetrates well into skin, both in healthy volunteers and in diabetic patients,4 while it is also found in satisfactory concentrations in experimentally