falsely elevated MICs for Acinetobacter spp., but resistant colonies were apparent even at 16 h in most strains that we tested.

None of the Australian carbapenem-resistant A. baumannii strains tested had an MIC low enough to suggest clinical utility for tigecycline. This is particularly disappointing because the isolates tested were those for which antibiotic choices are extremely limited and for which tigecycline would have been an attractive option. The propensity of A. baumannii to colonize the nosocomial environment and invasive medical devices, and be thereby exposed to antibiotic concentration gradients, raises concerns about whether tigecycline-resistant A. baumannii is likely to arise in vivo. This has been described in the Enterobacteriaceae and in A. baumannii, and our data further suggest that this will be the case. The phenomenon was consistent in multiple isolates of strains RB02 and PW01 (Table 1) and is unlikely to be unique to these isolates, as we have previously shown that strains WM96 and WM98 are closely related to the widespread A. baumannii EU clone II. Tigecycline is clearly a valuable addition to the formulary, but it should not be used against Gram-negative bacteria without prior susceptibility testing. Tigecycline resistance in A. baumannii appears to be stable and readily selected, pre-dates the use of the drug in this country and may be much more important than has been previously recognized. This may be especially true in strains exhibiting high-level resistance to multiple antibiotics, in which efflux systems may already be highly active.

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Transparency declarations

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References


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Voriconazole concentrations in synovial fluid and bone tissues

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Sir,

Voriconazole is now widely used for the treatment of a wide range of fungal infections, including invasive infections due to Aspergillus fumigatus. There have been a few case reports of voriconazole efficacy in bone and joint infections.1–4 However, voriconazole concentrations in these tissues were not reported. A medical case has given us the opportunity to measure voriconazole concentrations in an infected knee with an associated osteomyelitis.

An 83-year-old woman was referred to our department for arthritis of her left knee due to A. fumigatus. This was probably introduced during corticosteroid infiltration, several weeks before hospitalization. Before hospitalization in our department, drainage of her knee was performed and allowed joint fluid sampling. Because this yielded a high burden of Aspergillus, surgical debridement was performed with a washout and further drainage of the knee. During surgery, several biological samples were collected. Consecutive analysis demonstrated that the infection was present not only in the joint but also in the bone with resulting destruction of both the lower extremity of the femur and the upper extremity of the tibia. Owing to the massive destruction, and to the high Aspergillus burden, we decided with the patient and her family to perform an amputation above the knee.

MICs were determined using Etest (AB Biodisk, Solna, Sweden). The MICs of voriconazole and amphotericin B for the isolated strain were 0.012 mg/L and 0.75 mg/L, respectively.

The medical treatment of this patient consisted of voriconazole administration. It was begun before the debridement. She received a loading dose of 400 mg (6 mg/kg) intravenously every 12 h for 1 day and then 300 mg (4 mg/kg) twice daily intravenously for 3 days and then orally. As a result of this treatment, the fever resolved and the patient started to recover.
Unfortunately, she developed a severe sepsis with acute renal failure and died a few days after the amputation.

Two pairs of synovial fluid and serum samples (trough levels) were collected before the second dose of 400 mg of voriconazole (i.e. Day 1 of treatment), and before the second dose of 300 mg (i.e. Day 2 of treatment). Samples were immediately frozen at –20°C until analysis. Cortical and medullar bone samples were collected during the amputation (i.e. Day 6 of treatment). The patient medication did not involve drugs that could generate pharmacokinetic interactions with voriconazole. The patient had normal liver function and had a calculated creatinine clearance of 60 mL/min. The serum albumin concentration was low at 11.6 g/L (normal range: 38–46 g/L).

The measurement of voriconazole concentrations was performed using high-performance liquid chromatography coupled with a diode array detector method, as previously described and applied in our pharmacology department. For bone analysis, as there is no published analytical method for voriconazole assay in bone, previously published procedures for extraction in bone tissues were used to develop the assay method. The cortical bone samples were cut into small pieces. After addition of the analytical internal standard, 2 mL of 2 M acetic acid was added to 200 mg of cortical or medullar bone sample. The mixture was vigorously shaken for 10 min, boiled for 10 min and subsequently lyophilized. The stability of voriconazole through these extraction steps was verified. After addition of 500 µL of a saturated NH₄Cl/deionized water mixture (30/70, v/v) adjusted to pH 9.5 with 25% NH₄OH, voriconazole was assayed following the same procedure as for liquid samples. Calibration samples were obtained using voriconazole-free cortical or medullar bone samples and by means of appropriate addition of voriconazole solutions in order to obtain the following spiked bone sample concentrations: 0, 0.25, 1, 5, 10, 20 and 40 µg/g. The calibration curves were linear from 0.25 to 40 µg/g and the inter-assay precision coefficients of variation were lower than 15%.

Voriconazole concentrations in serum and synovial fluid were 2.41 and 0.76 mg/L on Day 1 and 4.09 and 1.07 mg/L on Day 2, respectively. Observed bone concentrations were 20.3 ± 2.41 and 0.76 mg/L on Day 1 and 4.09 and 1.07 mg/L on Day 2, respectively. The precision coefficients of variation were lower than 15%.

The serum concentrations were higher than those usually observed for this dosing. One explanation could be the low albumin serum level leading to an increase in the free voriconazole concentrations in serum (plasma protein binding of voriconazole is 58%). In the joint fluid, voriconazole concentrations were higher than the MIC for the isolated Aspergillus strain. In the bone, the concentrations were high and similar to those seen with fluoroquinolones or rifampicin, which are known as drugs having a good bone diffusion.

The concentrations of voriconazole in the synovial fluid and bone suggest that voriconazole may have a role in managing infections at these sites. Further studies are needed to confirm these results.

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**References**


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**Improving antimicrobial prescribing through knowledge and skills**

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Sir,

In their recent qualitative study of factors influencing antimicrobial prescribing by non-consultant hospital doctors De Souza et al. found that undergraduate education, hospital guidelines and concerns about emerging resistance were minor influences on prescribing practice. Prescribing was more influenced by instruction passed down through a hierarchical system and