Human platelets plus amphotericin B achieved significantly greater inhibition of the germination rate ($P<0.05$) than did amphotericin B or platelets alone (Figure 1a). The effect was additive. These results were found with both tested amphotericin B concentrations, although 1 mg/L revealed a better inhibitory effect than the lower concentration (Figure 1a). With caspofungin, the germination rate was not significantly reduced (Figure 1b). When azoles were used in combination with platelets, the inhibitory effect was found to be additive in comparison with either azole or platelets alone (Figure 1c and d). As found for the germination rate, human platelets plus amphotericin B achieved significantly greater inhibition of hyphal elongation ($P<0.05$) than amphotericin B or platelets alone. Hyphal elongation was significantly reduced in all tested aspergilli, either under platelet or caspofungin treatment. When used in combination, the effect was found to be additive. The combination of platelets plus either azole at any concentration tested did not significantly enhance the reduction of hyphal elongation. Platelets decreased the ability of hyphae to reduce XTT; however, the combination of platelets plus antimycotics had no additive effect on hyphal damage (data not shown).

Our findings indicate that platelets in combination with antimycotics exert additive effects in reducing the germination rate and hyphal elongation of *A. fumigatus* in vitro. Among the tested antimycotic substances, amphotericin B revealed the best results in combination with human platelets. However, platelets plus antimycotics were not additive for hyphal damage.

In the immunocompromised patient, inhaled *Aspergillus* conidia germinate into hyphae, the growing and invading structures of filamentous fungi. Consequently, blocking fungal germination and delaying hyphal growth is crucial in preventing invasive disease. In our study, the combination of platelets plus amphotericin B synergistically enhanced the antifungal activity ($P<0.05$) in reducing germination rate and hyphal elongation. Amphotericin B is known to complex with sterols in the fungal cell membrane, leading to pore formation and increased cell membrane permeability. This could support the antifungal activity of human platelets, by enabling the penetration of antifungal platelet factors.

A clinical study showed that patients with invasive fungal disease had a significantly longer duration of thrombocytopenia compared with those without infection, suggesting that the low platelet count is related to the infection. Our in vitro data suggest that a normal platelet count contributes to overcome fungal infections and that platelets are capable of enhancing the efficacy of antimycotics.

**Funding**

This work was supported in part by the grant MFI 2007412.

**Transparency declarations**

None to declare.

**References**


(J Antimicrob Chemother 2010; doi:10.1093/jac/dkq116
Advance publication 8 April 2010

**Should tigecycline be considered for urinary tract infections? A pharmacokinetic re-evaluation**

David E. Nix* and Kathryn R. Matthias

Pharmacy Practice and Science, University of Arizona, Tucson, AZ 85721, USA

*Corresponding author. Tel: +1-520-626-4814; Fax: +1-520-626-7355; E-mail: nix@pharmacy.arizona.edu

**Keywords:** urinary tract infections, tetracyclines, pharmacokinetics, multidrug resistance

Sir,

Recent debate over the use of tigecycline for urinary tract infection (UTI) treatment caused by multidrug-resistant (MDR) bacteria is based on concern of inadequate urine concentrations. First, a report of tigecycline effectiveness in a patient with recurrent UTI due to a presumed extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* isolate was published. The patient failed treatment with meropenem but the isolate from urine was reported susceptible to imipenem. The UTI was complicated by sepsis syndrome, renal abscesses, bilateral ureter catheters and possible pneumonia. A letter urging caution with the use of tigecycline for UTI treatment followed and summarized that only 15%--22% of tigecycline is excreted unchanged in urine. Although actual urine concentrations were not evaluated, the effect of renal impairment on tigecycline urinary excretion was discussed. The author asserted that "a 100 mg loading dose followed by 50 mg every 12 h does not ensure the ability to reach 1 to 2 mg/L in urine in a critically ill patient with chronic renal impairment." To our knowledge, urinary concentration data have not been reported in patients with renal failure beyond...
poster 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 x 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.5

References

J Antimicrob Chemother 2010
doi:10.1093/jac/dkq118
Advance publication 9 April 2010

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

Svenja K. Bahte1, Anna Bertram1, Olaf Burkhardt2, Jens Martens-Lobenhoffer3, Vega Goedecke1, Stefanie M. Bode-Böger3, Marcus Hiss1 and Jan T. Kielstein1*

1Department of Nephrology and Hypertension, Medical School Hannover, Hannover, Germany; 2Department of Pulmonary Medicine, Medical School Hannover, Hannover, Germany; 3Institute of Clinical Pharmacology, Otto-von-Guericke University of Magdeburg, Magdeburg, Germany

*Corresponding author. Tel: +49-511-532-6319;
Fax: +49-511-532-4005; E-mail: kielstein@yahoo.com

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. The treatment of peritoneal dialysis-associated peritonitis is becoming increasingly

Funding
No specific funding.

Transparency declarations
None to declare.