Lack of effect of extracorporeal membrane oxygenation on tigecycline pharmacokinetics

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Keywords: antibiotics, respiratory tract infections, RTIs

Sir,  
Extremely limited data are available on the pharmacokinetics of antimicrobial agents during extracorporeal membrane oxygenation (ECMO). We report the case of a young adult patient who was admitted on day 1 to our intensive care unit for acute respiratory failure due to intra-alveolar haemorrhage. Ventilator-acquired pneumonia due to Staphylococcus epidermidis and Staphylococcus warneri developed, initially treated with intravenous vancomycin. Despite maximal ventilator settings, optimal respiratory function could not be obtained, so veno-venous ECMO was started on day 38. The system comprised a membrane oxygenator (Quadrox Bioline, Jost-Maqueau, Orleans, France) and a centrifugal pump (Biomedicus 560, Medtronic, Minneapolis, MN, USA). Yet on day 50, respiratory conditions worsened. A persistent S. epidermidis pulmonary infection was observed, with induction of vancomycin resistance requiring antibiotic change to tigecycline on day 55. The patient’s renal function remained stable during hospital stay (CLCr 95 mL/min), but despite therapy and complete bacteria eradication the patient’s condition continued to deteriorate until death occurred on day 61. Tigecycline concentrations were measured by liquid chromatography–tandem mass spectrometry in plasma and tracheal aspirate.¹ The Berkeley Madonna software (v 8.3.18, University of California, Berkeley, CA, USA) was used to predict tigecycline concentrations using population mean parameter estimates from a previously published pharmacokinetic study in critical care patients.² The tigecycline dosing regimen and concentrations are presented in Table 1. Interestingly, concomitant tigecycline concentrations measured in plasma and aspirate were virtually identical.

The potential effect of ECMO on tigecycline pharmacokinetics had never been investigated before. Tigecycline is characterized by a large volume of distribution with a population mean value of 398 L in critical care patients,² which is therefore unlikely to be noticeably increased simply by dilution into the system, but adsorption on the circuit membranes could not be excluded.³,⁴ However, measured tigecycline plasma concentrations were virtually similar to the values predicted for a critically ill patient with CLCr = 95 mL/min and body surface area = 1.42 m²,² suggesting that ECMO has no effect on tigecycline pharmacokinetics.

Table 1. Plasma and tracheal aspirate concentrations of tigecycline administered intravenously at a dose of 50 mg twice daily simultaneously to ECMO

<table>
<thead>
<tr>
<th>Day 58, time since treatment initiation</th>
<th>Measured tigecycline concentrations</th>
<th>Predicted tigecycline concentrations from Rubino et al.²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 58, time since treatment initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma concentrations, mg/L (time since last dose)</td>
<td>0.50 (2.5 h)</td>
<td>0.31</td>
</tr>
<tr>
<td>Plasma concentrations, mg/L (time since last dose)</td>
<td>0.26 (8 h)</td>
<td>0.24</td>
</tr>
<tr>
<td>Plasma concentrations, mg/L (time since last dose)</td>
<td>0.21 (11 h)</td>
<td>0.22</td>
</tr>
<tr>
<td>Day 60, time since treatment initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma concentrations, mg/L (time since last dose)</td>
<td>0.20 (11 h)</td>
<td>0.23</td>
</tr>
<tr>
<td>Plasma concentrations, mg/L (time since last dose)</td>
<td>0.31 (4.5 h)</td>
<td>0.28</td>
</tr>
<tr>
<td>Aspirate concentrations, mg/L (time since last dose)</td>
<td>0.37 (5 h)</td>
<td>0.25</td>
</tr>
<tr>
<td>Plasma concentrations, mg/L (time since last dose)</td>
<td>0.26 (8 h)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

References


J Antimicrob Chemother 2012  
doi:10.1093/jac/dkr550  
Advance Access publication 29 December 2011
Funding
Support was only provided by institutional sources.

Transparency declarations
None to declare.

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J Antimicrob Chemother 2012
doi:10.1093/jac/dkr556
Advance Access publication 29 December 2011

More about the safety of tigecycline for the treatment of infectious diseases: the role of superinfection rates

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Keywords: multidrug resistant, glycylcyclines, Pseudomonas aeruginosa

Sir,

We have read with great interest papers published concerning the efficacy and safety of tigecycline and the ensuing correspondence. Mortality has been reported in most of the publications to be higher with tigecycline in comparison with other antimicrobial agents. However, we would like to make some remarks on the role of superinfection rates during treatment with tigecycline, and the impact on safety.

Tigecycline was approved by the US FDA for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections (2005), and for community-acquired pneumonia (2009). Due to the high rates of multidrug-resistant (MDR) pathogens and the scarcity of new antibacterial agents, the use of tigecycline was extended to the treatment of colistin-resistant Acinetobacter baumannii infections, and as an alternative for patients allergic to β-lactam antimicrobial agents, by the Commission of Infections and Antimicrobial Policy in our hospital.

In January 2010 the FDA warned against using tigecycline in pulmonary infections because of increased mortality risk.1 A recently published meta-analysis2 concluded that tigecycline is not better than standard antimicrobial agents for the treatment of serious infections. Mortality from all causes was higher in the tigecycline group, although the difference was not statistically significant. On the other hand, they reported that an important advantage of tigecycline is that it can be used as monotherapy because it has a broad spectrum of antimicrobial activity. Despite this, their meta-analysis focused on randomized trials of only a few MDR infections.

Tigecycline has broad-spectrum in vitro activity against methicillin-resistant Staphylococcus, penicillin-resistant Streptococcus pneumoniae, vancomycin-resistant Enterococcus spp. and most Enterobacteriaceae, including extended-spectrum β-lactamase-producing strains. Tigecycline is also active against A. baumannii, including MDR strains. Proteus spp., Providencia spp., Morganella spp. and Stenotrophomonas maltophilia have reduced susceptibility. Pseudomonas aeruginosa is intrinsically resistant.

In order to evaluate the rate of superinfections due to the emergence of tigecycline resistance, we performed a retrospective and observational study of 51 patients treated with tigecycline.3 The overall 30 day mortality was 23.5% (12/51). The superinfection rate during tigecycline treatment was 23.5% (12/51), with P. aeruginosa being responsible for 58.3% (7/12) of the superinfections.

With the aim of confirming these results, we extended the cohort in a prospective study (1 November 2008 to 31 January 2010). Tigecycline was prescribed as the treatment for nosocomial infections in 74 patients in this period. The method and definitions for this study were the same as those used in the previous study.3 The overall 30 day mortality was 28.4% (21/74). The superinfection rate during tigecycline treatment was 24.3% (18/74), with P. aeruginosa being responsible for 33.3% (6/18) of the superinfections.

In the overall results, superinfection was observed in 24.0% (30/125) of the patients treated with tigecycline. P. aeruginosa was isolated in 13 patients (10.4%); the other 17 superinfections (13.6%) were caused by Proteus mirabilis (4), Enterobacter cloacae, Morganella morgani (2), Enterococcus faecalis (2), Providencia stuartii, Klebsiella pneumoniae (5), Escherichia coli and S. maltophilia. The characteristics and outcomes of the 30 patients with superinfections are detailed in Table 1. Nine patients with superinfections died (30.0%).

The data collected during the 27 months of our study suggest that tigecycline may increase the number of superinfections caused by intrinsically resistant microorganisms (e.g. P. aeruginosa) or by microorganisms with reduced susceptibility to tigecycline (e.g. Proteus spp., K. pneumoniae, S. maltophilia, M. morgani, Enterobacter spp.).