Correspondence

Sir,

My recent leading article1 on silver-based products as antimicrobial agents was intended primarily to address microbiological issues such as bacterial susceptibility and the potential for the development of resistance to these products. Consequently, I did not consider the toxicological issues raised by Bayston et al.2 in their comment upon my article.

Obviously, a heavy-metal cation such as silver has the potential to inhibit processes in mammalian cells and as noted by Bayston et al.,2 various forms of silver-associated toxicity have been reported, although fortunately they are rare in clinical practice. Experience with antibiotics tells us that dosing with sub-MIC levels creates conditions favourable for the selection of resistant organisms. Applying these principles to the silver situation led me to conclude that products releasing high levels of silver were unlikely to generate conditions for the selection of silver-resistant microorganisms. However, I agree with Bayston et al.2 that the use of such products could pose a greater risk of toxicity than low silver release formulations and that the therapeutic index for silver-based products may be rather low.

Concerning the issue of zones of inhibition raised by Bayston et al.,2 it may well be true that free silver ions capable of diffusion are not released from nanoparticle systems. Unfortunately, the abstract,3 cited by Bayston et al.,2 does not appear to support this claim. No zones of microbial inhibition were observed with the silver-impregnated catheters used by the authors,1 implying no diffusion of free silver ions from the catheter material. However, there appeared to be insufficient silver in this product even to affect the viability of bacteria (Staphylococcus epidermidis) bound to the catheter surface. Consequently, it is difficult for Bayston et al.2 to argue from these data3 that organisms attached to the surface of the catheter can be killed by silver in the absence of diffusion of the cation from the device.

Transparency declarations

The author received an educational grant from Smith and Nephew Research to review the literature and prepare the published leading article.1

References


Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkm199
Advance Access publication 7 June 2007

Does pre-treatment with lamivudine prime for adefovir resistance of hepatitis B virus infection?

Hüseyin Sirma1, Anneke Funk1, Wolfram Gerlich2 and Oliver Schildgen3*

1Heinrich-Pette-Institute, Hamburg, Germany; 2Institute of Medical Virology, University of Giessen, Germany; 3Institute for Medical Microbiology, Immunology, and Parasitology, University of Bonn, Sigmund-Freud-Strasse 25, D-53105 Bonn, Germany

Keywords: antiviral therapy, HBV, resistance

Sir,

We read the recent case report by Ni Laoi et al.1 with great interest. The authors report on a chronic hepatitis B virus (HBV) infection resistant to lamivudine and adefovir. During antiviral therapy, lamivudine was replaced by adefovir due to the emergence of resistant virus. The subsequent therapy with adefovir was ineffective and did not decrease the viraemia to a significant extent despite reliable compliance. Analysis of the virus genomes did not reveal any mutation known to be associated with adefovir resistance, but the previous treatment with lamivudine had induced the mutation rtA181V. Mutation at this position is reported to confer resistance to lamivudine and the rtA181T exchange is suspected to mediate adefovir resistance although the experimental proof is still lacking.

In our view, the report by Ni Laoi et al.1 in concert with earlier publications2–8 underscores the urgent need for a paradigm change in antiviral therapy of chronic HBV for the following two reasons: (i) it reflects an increasing problem; and (ii) cases of initial non-response to antiviral drugs occur frequently rather than being rare events. Thus, the initial non-response to antiviral therapy is only the peak of an iceberg whose extent is not fully known. The list of mutations mediating resistance to antiviral therapy is far from being complete. The increasing number of reverse transcriptase (RT) inhibitors licensed for antiviral therapy will further increase both the number and complexity of resistance mutations. These issues are of great medical importance since they might result in emergence of mutant viruses escaping vaccine protection and diagnosis. Thus, we fully support the recommendation by Ni Laoi et al.1 that genotypic analysis and sequencing of the RT polymerase domain of the HBV strains should become a routine part of an individualized antiviral therapy. Also, the role of host factors contributing to drug resistance such as cellular metabolic (dys-)functions9 should be elucidated. To defeat the problem of resistance mutations and its consequences, we would like to propose a systematic approach for data monitoring and mining of therapy in HBV antiviral resistance. This approach should combine present and future knowledge and experience and requires union of both national and international forces and groups active in the field.

Transparency declarations

None to declare.

448
Correspondence

Sir, In the April 2007 issue of the Journal of Antimicrobial Chemotherapy, Navon-Venezia et al.1 reported high resistance rates to tigecycline in multiple clones of multidrug-resistant (MDR) Acinetobacter baumannii (n = 82). The authors found that 66% (54/82) were resistant to tigecycline (MIC ≥8 mg/L), 12% (10/82) were intermediate (MIC 4–6 mg/L) and 22% (18/82) were susceptible (MIC ≤2 mg/L). They used Etest to determine MICs and all the values correlated 100% with inhibition zone diameters using the disc diffusion method with tigecycline discs.1

We agree with the authors that MDR in Acinetobacter spp. represents a global challenge to physicians; for this reason we will try to offer a wider point of view.

The Tigecycline Evaluation and Surveillance Trial (TEST) is a worldwide programme that includes, at the moment, 4247 isolates of Acinetobacter spp. of which only 2% have a tigecycline MIC ≥2 mg/L.2

Based on this data, we compare the results of Navon-Venezia et al.1 with those of TEST, using the global data and the Argentinean sub-set data. We selected from the TEST database the isolates of MDR A. baumannii with the same resistance profile as those analysed by Navon-Venezia et al.1 (i.e. A. baumannii resistant to aminoglycosides, cephalosporins and fluoroquinolones) (Table 1).

In contrast with the 78% published by Navon-Venezia et al.,1 only 5.3% of the global isolates and 2% of the Argentinean sub-set isolates of MDR A. baumannii in TEST had tigecycline MICs ≥2 mg/L. We asked ourselves what would be the probability of encountering such a difference if all the isolates belong to the same population. We performed a proportion test to do so. The probability was very low (P < 0.0001).

Regarding the MDR A. baumannii isolates as previously defined, and additionally resistant or intermediate to imipenem, the resistance ratio to tigecycline showed important differences (95%, 5.6% and 0% for Navon-Venezia et al.,1 TEST global2 and Argentinean sub-set,2 respectively).

Tigecycline has been approved for the treatment of complicated intra-abdominal infections and complicated skin and skin

Table 1. Comparison of susceptibility rates to tigecycline in MDR A. baumannii

<table>
<thead>
<tr>
<th>Isolates</th>
<th>TEST global</th>
<th>TEST Argentina</th>
<th>Navon-Venezia et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>377</td>
<td>48</td>
<td>82</td>
</tr>
<tr>
<td>TIG MIC ≥2 mg/Lb</td>
<td>20 (5.3%; 2.9–7.7%)</td>
<td>1 (2%; 0–7.16%)</td>
<td>64 (78%; 68.48–87.62%)</td>
</tr>
<tr>
<td>Method</td>
<td>microdilution</td>
<td>microdilution</td>
<td>Etest</td>
</tr>
<tr>
<td>IPM-R/I</td>
<td>178</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>TIG MIC ≥2 mg/Lb</td>
<td>10 (5.6%; 1.95–9.28%)</td>
<td>0 (0%; 0–1.78%)</td>
<td>21 (95%; 84.48–100%)</td>
</tr>
<tr>
<td>Method</td>
<td>microdilution</td>
<td>microdilution</td>
<td>Etest</td>
</tr>
</tbody>
</table>

MDR, multidrug-resistant; TEST, Tigecycline Evaluation and Surveillance Trial; TIG, tigecycline; IPM, imipenem; R/I, resistant/intermediate.

*Corresponding author. Tel: +54-11-4567-4426; Fax: +54-11-4822-2748; E-mail: djcurcio@gmail.com or infectologia.institucional@gmail.net.ar

References