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Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkm203
Advance Access publication 4 June 2007

Comment on: The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern?

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Keywords: biomaterials, toxicity, infection

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Sir,

We read the article by Chopra1 on the increasing use of silver-based products with interest and we would like to make some observations.

The title of the article asked whether there was cause for concern, and, understandably, the issue of resistance was raised in this respect. Chopra makes a case for using dressings that release high concentrations of silver in order to overcome this, yet, in certain circumstances, this could raise the possibility of toxicity. Silver-processed products range from wound dressings to catheters, and the individual exposure to silver will vary enormously. Systemic toxicity (argyria) is rare but has been reported after topical use.2,3 Although reports of actual morbidity due to argyria are rare, neuropathy has been reported from topical use and from the use of silver in bone cement.4–3 Of equal concern is the selective deposition of silver in the CNS5–7 associated with the use of intracranial catheters, two of which are now available (Silverline, Spiegelberg GmbH; Vygon Expert, Vygon GmbH). In addition, local cytotoxicity has been demonstrated8 when silver-coated implants have been evaluated. It appears that the window between minimum concentrations lethal to microbes and those lethal to host cells is narrow and is easily missed in practice. In most cases this will not be clinically important, but in some it will be.

The design of the silver release system is also important. For example, if the aim is to kill microbes that impinge on the device, such as in a catheter, then low rates of release of silver ions from perhaps a nanoparticle system9 might suffice, but if the effect of silver is to be exerted in the surrounding tissue or exudates, as in a dressing, then greater amounts of silver must be released and this might be best in the form of a silver salt.

Finally, Chopra discussed the zones of inhibition expected from silver systems, yet one would not see a zone of inhibition from a nanoparticle system despite its ability to kill attached microbes,11 but one might with a silver salt system. The diversity of silver systems available and the often inadequate understanding of their modes of action have in our view led to confusion over the clinical efficacy of silver. Chopra’s article is timely in that it raises the issue and hopefully will stimulate debate.

Transparency declarations

None of the authors has received financial or other support in connection with this research.

References


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Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkm224
Advance Access publication 18 June 2007

The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern?—author’s response

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Keywords: silver, toxicity, susceptibility

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Sir,
My recent leading article 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 data\(^3\) 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


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

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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 publications\(^2\)–\(^8\) 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-) functions\(^9\) 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.