Is Vancomycin Ototoxicity a Significant Risk?

Forouzesh and colleagues recently reported an increase in vancomycin ototoxicity in parallel with the increasing use of higher vancomycin doses (4). The report suggests an overall incidence of vancomycin-induced ototoxicity of 12%, doubling historic estimates (3). This is a surprisingly high estimate for a drug that many experts do not consider to be ototoxic (5, 6). The authors have outlined several limitations to their nonrandomized, retrospective review, yet several other limitations must be taken into consideration.

First, the premise of this study was to highlight the importance of toxicity during an era of aggressive dosing for vancomycin. The authors have reported vancomycin ototoxicity to be dose dependent as justification for their review; however, this is contrary to consensus guidelines that have recently been published (5). Serum vancomycin levels do not correlate with ototoxicity, presumably why the authors found no differences in vancomycin trough levels between patients with and without hearing impairment. Similarly, the vancomycin doses for the patients with audiogram changes do not reflect a more aggressive dosing trend at this institution. Only one patient received more than 2 grams of vancomycin per day and that patient had a range of vancomycin trough levels of 8.8 to 9.8 mg/liter. This pattern of vancomycin prescribing should not be considered a reflection of the era of increasing doses.

Second, the authors have documented hearing impairment on an ordinal scale, defining categories as normal, mild, moderate, severe, and profound. However, Table 3 in the study of Forouzesh et al. (4) makes reference to categories that have not been defined, such as mild to moderate. This type of scale is also misleading. For instance, a patient may have a change of 2 decibels (dB) from baseline to follow-up but still meet the definition for a worsening audiogram. This is significant, because a change of ±5 dB is normal variability in an alert, oriented patient (1). Similarly, there can be variability in the instrumentation used; a confounder may produce evidence of hearing loss by technical failure alone (2). Certainly, tremendous variability is possible given these inconsistencies in combination with background noise and the use of ordinal categories to report results. Categorizing hearing loss is not an accurate method of measuring the ototoxic effects of a drug; instead it is suggested to report a change from baseline to follow-up. This has been reported previously, using a change of 30 dB, at any frequency, to define hearing loss (3).

Third, the inclusion of patients on concomitant ototoxic medications does not allow for an unbiased evaluation on the effects of vancomycin. The exclusion of the three patients who received additional ototoxic agents decreases the incidence of vancomycin-induced ototoxicity from 12% to 8.9%.

It is agreed that ototoxicity from antibiotics has potential quality-of-life implications, as the authors allude, but we find it difficult to assess these implications given the methodology used. Because baseline audiometry is not routine in most facilities, it is important to provide a clinical evaluation of the patients included in this study to extrapolate the results. Undoubtedly, a control group is necessary to elicit a more accurate assessment of the ototoxic effects of vancomycin. Further studies are clearly needed to control for previously mentioned variables to predict an accurate incidence of vancomycin ototoxicity and associated determinants of risk. While an investigation in the modern era is indeed warranted, the conclusion of a significant risk is not.

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REFERENCES


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Authors’ Reply

We greatly appreciate the comments on our article “Vancomycin ototoxicity: a reevaluation in an era of increasing doses” (2) offered in the above letter by R. Shields et al. We agree that the actual doses used in this study were not necessarily above historical standards and therefore suggest that our article may have been more appropriately titled “Vancomycin ototoxicity: a reevaluation in an era of increasing pharmacokinetic exposures.” Higher pharmacokinetic exposures are to be expected in patients who are older and with reduced creatinine clearance that are administered conventional vancomycin doses, as was the general case in our patient population.

Shields et al. have specified limitations inherent to audiolog testing and the reporting of these results, particularly as to definitions of the semiquantitative categories of the audiogram results of the 11 patients with worsening audiograms in Table 3 of the article (2). The mixed categories (e.g., mild-moderate hearing loss) referred to patients whose ability to hear at different frequencies spanned two categories of hearing impairment across the spectrum tested. For example, a patient with mild impairment across low frequencies and moderate impairment across high frequencies would be labeled as “mild-moderate” hearing loss. A patient with moderate impairment across low frequencies and severe impairment across high frequencies would be labeled as “moderate-severe” hearing loss.

To address their third comment, we noted no difference in the frequency of patients receiving concomitant ototoxic medications in the group of 11 patients who developed worsening...
audiograms versus the 78 patients who did not. In fact, two of the three patients who were on the potentially ototoxic furosemide and developed worsening audiograms were on furosemide for some length of time prior to exposure to vancomycin (as indicated in the footnote to the table in the paper), and we assume it unlikely that the worsening audiograms were directly attributable to furosemide. Whether there may be an additive ototoxic consequence of concomitant furosemide and vancomycin is unknown and cannot be answered in this study. However, given the frequency of the concomitant use of both furosemide and vancomycin, a study that answers this question would be of great clinical interest.

The current management of gram-positive infections, particularly of methicillin-resistant *Staphylococcus aureus* (MRSA) is seeing unprecedented patient exposures to glycopeptides in order to chase reduced susceptibilities to glycopeptides seen among clinical *S. aureus* isolates (8). Despite the great numbers of patients on vancomycin, real-world and particularly contemporary human data on the ototoxic effects of the drug are quite sparse, including the data referenced in the current vancomycin consensus statement (7). Increased vancomycin exposure (i.e., serum troughs of 15 to 20 mg/liter) are recommended for preventing further vancomycin heteroresistance among *S. aureus* and/or for increasing therapeutic efficacy through pharmacodynamic target achievement of an area under the concentration-time curve or MIC of 400 (1, 7). Note that this recommended target for serious MRSA infections is based only on retrospective data from pneumonia (6), not for bacteremia, osteomyelitis, or meningitis infections to which it has been extrapolated in the guidelines, and that this pharmacodynamic target is unachievable by recommended dosing against MRSA with vancomycin MICs of 2 mg/liter (7). In fact, increasing vancomycin pharmacokinetic exposure has yet to be shown to increase efficacy, and several studies have pointed out potential risks of nephrotoxicity (3–5). The doubling of historical estimates of ototoxicity in our study should be viewed as exactly as stated in the letter by Shields, an estimate (2).

The lack of availability of audiograms for most clinicians does not justify increasing patient pharmacokinetic exposures to vancomycin with little concern for potential ototoxicity. Given the inherent limitations of evaluating ototoxicity in this setting and the fact that our institution provided a fairly unique opportunity to evaluate audiogram data in patients treated with vancomycin, the purpose of our study was to open the door of scientific discourse and the further study of the potential ototoxicity of vancomycin with higher pharmacokinetic exposures. The letter by Shields et al. is encouraging the opening of this door. A prospective study is needed to more closely examine this issue.

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REFERENCES


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