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**Negative Results Do Not Imply Absence of Ototoxicity with Middle Ear Application of Neomycin**

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What is This?
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In the February edition of this journal, Dr James House and Ms Laura House reported on hearing outcomes with the use of neomycin/polymyxin B/hydrocortisone (PNH) suspension in patients who underwent tympanoplasty.1 The authors found no significant changes in bone conduction at 500 to 4000 Hz in 272 patients. They concluded that PNH is not associated with ototoxicity and is safe to use in tympanoplasty. The authors contrasted their findings with our study of 134,598 children with nonintact tympanic membranes, in which we found an association of repeated doses of neomycin ear drops with sensorineural hearing loss (SNHL).2 However, the authors may have missed several important explanations for the apparent discrepancy.

First, 272 patients were insufficient to study the association of topical neomycin with SNHL, which has an incidence of less than 1 in 1000.3 House’s study was powered to show that the rate of ototoxicity was less than 1 in 90.3 Second, the House study addressed a very limited exposure of the inner ear to PNH. The volume of the human middle ear is roughly 0.5 mL.4 Thus, the inner ear exposure was equivalent to 1 day of ototopical therapy (5 drops/dose × 0.05 mL/drop × 2 doses/day). The finding of no ototoxicity with such limited exposure is entirely consistent with our findings when restricting analyses to the first dispensed vial (hazard ratio [HR] = 0.90; 95% confidence interval [CI], 0.76-1.07). Third, we disagree with House’s claim that our results might be invalid because no audiometric data were examined. In fact, each confirmed case in our study had at least 1 billed procedure for audiometry that was performed within 1 month before their SNHL diagnosis. If some diagnoses were made erroneously, false positive cases would bias our results toward the null hypothesis (ie, no ototoxicity). Finally, House pointed out that children who had ≥ 3 doses of neomycin eardrops in our study had a slightly lower association with SNHL than those who received 2 doses, suggesting inconsistent results. However, the confidence intervals of these estimates overlap considerably, mainly due to the small number of cases in the group with ≥ 3 doses (HR = 1.45; 95% CI, 1.05-2.01 vs HR = 1.30; 95% CI, 0.71-2.36). Therefore, we cannot conclude that these 2 point estimates are significantly different from each other.

It is important that clinicians clearly understand these issues before applying PNH to the middle ear.

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