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EDITORIAL

Use of Ototoxic Medications in Neonates—The Need for Follow-Up Hearing Test

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In 2007, the American Academy of Pediatrics (AAP) published a position statement regarding hearing screening in neonates which stated that "all infants with a risk indicator for hearing loss, regardless of surveillance findings, should be referred for an audiological assessment at least once by 24 to 30 months of age." One of the risk indicators that the AAP referred to includes exposure to ototoxic medications such as aminoglycosides and loop diuretics during the neonatal period. This 2007 statement contradicts the 2000 position, which states that hearing screening is not required following exposure to ototoxic medications since the risk of hearing loss associated with such an exposure is small (1.5%).[2]

The current literature indicates that the incidence of aminoglycoside-associated hearing loss is very low. McCracken and colleagues conducted a 2 to 6 year study of 79 neonates who received gentamicin for bacterial meningitis.[3] Only 1.3% of the cohort had evidence of hearing impairment. Another prospective study from 1990 to 1997 evaluated 820 patients who had received aminoglycosides during the neonatal period.[4] Hearing was then evaluated by either the transient evoked otoacoustic emissions (TEOAE) or the brainstem evoked response audiometry (BERA). Only 13 (1.6%) of these patients had documented sensorineural hearing loss (SNHL), and 11 of these 13 individuals had other risk factors that predisposed them to hearing impairment (e.g., family history of hearing loss). Not only is the incidence of aminoglycosides-associated hearing impairment low, the risk in neonates is less than that noted in adults and adolescents.[5] The incidence of hearing loss attributed to the loop diuretics is unknown. Bumetanide seems to cause less hearing impairment when compared to furosemide.[6] Although the mechanism is unknown, the difference may be due to the longer half-life of furosemide in neonates.[7]

ABBREVIATIONS AAP, American Academy of Pediatrics; BERA, brainstem evoked response audiometry; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; SD, standard deviation; SNHL, sensorineural hearing loss; TEOAE, transient evoked otoacoustic emissions

The newest AAP recommendation is principally based on the article by Fligor and colleagues regarding factors associated with SNHL in patients who were on extracorporeal membrane oxygenation (ECMO) during the neonatal period.[1,8] This study concluded that ECMO graduates who were on an extensive course of aminoglycosides were at an increased risk of developing SNHL. These conclusions require careful evaluation.

The authors appropriately reported that the "treatment factor data [of the study] were highly skewed".[8] Because of this variance some of their treatment factors (e.g., total days of aminoglycoside therapy) should have been reported as median instead of mean. There is a high possibility that the majority of patients who developed SNHL may not have received antibiotics for a long duration. A few patients who did receive antibiotic for an extended period may have

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inappropriately influenced the conclusions. The standard deviation (SD) associated with the mean values (resulting in negative integers) actually verify this point. The same problem can be seen with the confidence interval for the hazard ratio for the aminoglycosides reported in the COX regression analysis. If an endpoint contains negative value, when taking SD into account, one should question the statistical method used.

One of the concerns raised by the authors in this article is that aminoglycosides may cause delayed-onset SNHL.[8] For this reason the AAP recommends a repeat hearing test by 24 to 30 months of age.[1] This study, however, did not prove that aminoglycosides can cause delayed-onset SNHL. Delayed-onset SNHL was defined in this study as "a patient having ≥ 1 diagnostic audiologic evaluation indicating normal hearing across all frequencies tested and subsequent evaluations confirming the presence of SNHL."[8] A protocol was originally established to require a hearing test at discharge and at age 12, 18, 30, and 42 months; however, as illustrated by Table 5 in the article, follow-up hearing tests were obtained at any time and were "variable among subjects."[8] If that were the case, some of these individuals who had delayed-onset SNHL might have already developed hearing loss before their audiologic examination. Also, the authors did not report when the last dose of aminoglycosides was administered to the patient before the hearing tests were performed. There was not any correlation between the time of last dose of aminoglycosides administered and the development of hearing loss. In fact, a review of the available data does not allow one to decipher if the delayed onset of SNHL was mainly caused by the duration of ECMO, history of congenital diaphragmatic hernia (CDH), or duration of aminoglycoside therapy.

One may argue that the Kaplan Meier curve presented in the article clearly proves that there is a delay onset of hearing loss associated with aminoglycosides, especially in the group who received therapy for less than 14 days. This observation, however, is invalid. First, patients with hearing loss might actually have acquired impairment before they were diagnosed. It all depends on the age of the child's first hearing screening. Ototoxicity associated with aminoglycosides usually occurs within weeks, not years, after the initiation of therapy.[9,10] An animal study showed that the hair cells density of chinchilla's neuroepithelium in the crista of the vestibular system significantly reduced 2-weeks after treating with a 6-day course of gentamicin (30 mg/kg/day), but this density normalized after 3 weeks.[11] Since chinchilla ear anatomy is similar to human ears, there is a possibility that humans also possess this capability of self repair after exposure to aminoglycosides.

A major flaw of the Fligor study is that aminoglycoside serum concentrations were not reported in the patients.[8] Supratherapeutic concentrations of aminoglycosides have repeatedly been shown to increase a patient's risk of ototoxicity.[4,12,13] Since concentrations were not monitored in this study, there is a high possibility that those patients who developed SNHL actually had supratherapeutic serum concentrations while on aminoglycosides. If patients had elevated serum concentrations, without question they would have an increased risk of developing ototoxicity, especially if therapy was given for a prolonged period of time. The significant hazard ratio reported when those who received treatment < 14 days were compared to those given therapy ≥ 14 days would suggest this might have been the case. The higher incidence of hearing loss (~26%) in this study, compared to other studies (1%-3%), can also possibly be explained by this argument.[8]

Other studies have proven that aminoglycosides are not a risk factor for hearing loss. In a study by de Hoog and colleagues, 508 neonates exposed to tobramycin were evaluated on their auditory function 2 weeks after discontinuation of the antibiotic.[14] Four hundred seventy three subjects passed their hearing examination and the antibiotic was not associated with an increased risk of hearing loss ($p = 0.19$).

A prospective, longitudinal study also evaluated the association of aminoglycosides with SNHL.[15] Eighty-one subjects who had received aminoglycosides as neonates (both near-term and term) were included in this study. The objective of this study was to evaluate its 4-year SNHL risk. This study did not find any significant relationship between SNHL and cumulative aminoglycoside dose (>28 mg/kg), average dose per day (> 4 mg/kg/day), and duration used (>7 days).[15] In another prospective, randomized study, 347 newborns were given either gentamicin 5 to 6 mg/kg/day, kanamycin 15 mg/kg/day, or placebo.[9] Baseline characteristics were similar and

serum concentrations were monitored. Patients were followed for a total of 4 years. At the end of the study period, there was no significant difference in the incidence of SNHL, vestibular dysfunction, and psycholinguistic difficulties among the three groups.

The study by Fligor et al. also indicated that patients with SNHL were on loop diuretics for a longer period of time, but this finding did not reach statistical significance.[8] Ototoxicity associated with loop diuretics is actually related to the rate of medication administration and not to the medication itself. In a randomized, crossover study, patients were given either a furosemide intravenous bolus injection (given over 5 minutes) or an 8-hr furosemide infusion.[16] The bolus dose was associated with a significantly higher serum concentration of the medication when compared to the infusion (95 ± 20 mg/L vs. 24 ± 5 mg/L, respectively) ($p < 0.0001$). Five patients had reversible hearing loss with the bolus administration.[16] Rapid bolus administration of furosemide is associated with increased risk of ototoxicity due to the high serum concentration (>50-100 mg/L) resulting from the rate of administration.[16] Slow administration at a rate of ≤ 4 mg/min can actually prevent this adverse effect.[17] If a bolus dose is required, it should be administered at 0.5 mg/kg/min if the dose is < 120 mg or at least 4 mg/min if the dose is ≥ 120 mg.

Based on all these data, evidence is not strong enough to require all neonates who were on aminoglycosides or loop diuretics during their neonatal period to have a follow-up hearing screening at 24 to 36 months of age because aminoglycosides have not been shown to cause delayed SNHL and ototoxicity associated with furosemide can be prevented by administering the medication slowly or via an infusion. Lastly, a follow-up hearing screening as recommended by the AAP is often not covered by insurance, which will create a financial burden on the patient's family.

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REFERENCES

1. Joint Committee on infant hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics 2007;120:898-921.
2. Joint Committee on Infant Hearing. Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics 2000;106:798-817.
3. McCracken GH, Mize SG. A controlled study of intrathecal antibiotic therapy in gram negative enteric meningitis of infancy. J Pediatr 1976;89:66-72.
4. Hess M, Finckh-Kramer U, Bartsch M, et al. Hearing screening in at-risk neonate cohort. Int J Pediatr Otorhinolaryngol 1998;46:81-89.
5. Aust G. Vestibulotoxicity and ototoxicity of gentamicin in newborns at risk. Int Tinnitus J 2001;7:27-29.
6. Rybak LP. Pathophysiology of furosemide ototoxicity. J Otolaryngol 1982;11:127-133.
7. Wells TG. The pharmacology and therapeutics of diuretics in the pediatric patient. Ped Clin North Am 1990;37:463-504.
8. Fligor BJ, Neault MW, Mullen CH, et al. Factors associated with sensorineural hearing loss among survivors of extracorporeal membrane oxygenation therapy. Pediatrics 2005;115:1519-1528.
9. Hieber TF, McCracken GH, Roeser RJ, et al. Ototoxicity in neonates treated with gentamicin and kanamycin: results of a four-year controlled follow-up study. Pediatrics 1979;63:443-450.
10. Beaubien AR, Desjardins S, Ormsby E, et al. Delay in hearing loss following drug administration. Acta Otolaryngol 1990;109:345-352.
11. Tanyeri H, Lopez I, Hoffman L. Time dependent changes in the crista neuroepithelium resulting from gentamicin ototoxicity in the chinchilla. Tr J Med Sci 1999;29:211-218.

12. Black RE, Lau WK, Weinstein RJ, et al. Ototoxicity of amikaicin. Antimicrobial agents and chemotherapy 1976;9:956-961.
13. Echeverria P, Fina D, Norton S. Ototoxicity of gentamicin: clinical experience in a children's hospital. Chemotherapy 1978;24:267-271.
14. de Hoog M, van Zanten BA, Hop WC, et al. Newborn hearing screening: tobramycin and vancomycin are not risk factors for hearing loss. J Pediatr 2003;142:41-46.
15. Robertson CMT, Tyebkhan JM, Peliowski A, et al. Ototoxic drugs and sensorineural hearing loss following severe neonatal respiratory failure. Acta Paediatrica 2006;85:214-223.
16. Dormans TPJ, van Meyel JJM, Gerlag PGG, et al. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cariol 1996;28:376-382.
17. Rupp W. Pharmacokinetics and pharmacodynamics of lasix. Scot Med J 1984;19(suppl):5-13.