

MOTHERISK ROUNDS

Is Gentamicin Ototoxic to the Fetus?

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Abstract

Background: Gentamicin is used in pregnancy to treat infections that cause complications to the mother and fetus if left untreated. In 2003, Schering, the manufacturer of Garamycin Injectable, amended the product monograph in the Compendium of Pharmaceuticals and Specialties to state that gentamicin should be avoided in pregnancy due to cases of "total irreversible bilateral congenital deafness" in babies exposed to gentamicin in utero. Because we have identified, after an intensive literature search, only two cases over many years of availability, it is questionable whether the outcome can be attributed to drug use rather than other factors.

Objectives: The main objective of this study was to determine whether any infant exposed in utero to intravenous gentamicin and born between January 2002 and April 2006 at Victoria General Hospital demonstrated audiologic deficits on routine hearing testing. Such testing has been universally available since late 2001. Our secondary objectives were to examine patterns of gentamicin use, including indication, dosage, duration, and to determine whether or not monitoring of serum gentamicin levels was done.

Methods: Women who had received gentamicin were identified through pharmacy records and their charts reviewed for factors that might contribute to fetal deafness including substance abuse, use of other potentially ototoxic medications, genetic predisposition, and intrauterine infections. We reviewed audiology test result and the infants' charts for potential confounding factors, including prematurity, low birth weight, low Apgar scores, anoxia, hyperbilirubinemia, sepsis, and meningitis.

Results: Fifty-two charts were reviewed, 40 of which documented live births. There was no case of hearing loss documented. Of the eight fetal losses, six (11.5%) were preterm births before viability, and two were elective terminations. Pyelonephritis was the main indication for gentamicin use (48%), followed by chorioamnionitis (31%) and other miscellaneous indications (21%). Three times

daily dosing was used for a mean duration of 2.7 ± 2.3 days, resulting in an average cumulative dose of 764 ± 600 mg gentamicin. The average gestational age at exposure was 28 weeks. Maternal serum gentamicin levels were obtained in 72.5% of cases, and no trough level was above 2 mg/L. Other potentially ototoxic medications were administered to the mother in 17.5% of pregnancies, and to 17.5% of babies in the immediate newborn period. With the exception of one infant who died before additional testing could be carried out, all the infants passed hearing tests, 89% on initial screening.

Conclusion: In utero exposure to gentamicin did not cause an increase in audiologic impairment in the infants tested in this cohort.

Résumé

Contexte : La gentamicine est utilisée au cours de la grossesse pour la prise en charge des infections qui, sinon, causent des complications à la mère et au fœtus. En 2003, le fabricant de Garamycin Injectable, Schering, a modifié la monographie de produit apparaissant dans le Compendium des produits et spécialités pharmaceutiques, de façon à ce qu'elle indique que la gentamicine devrait être évitée au cours de la grossesse en raison du signalement de cas de « surdité congénitale bilatérale irréversible totale » chez des nouveau-nés exposés à la gentamicine *in utero*. Puisque nous n'avons identifié, à la suite d'une recherche documentaire intensive, que deux cas sur une période couvrant de nombreuses années, nous considérons que le fait d'en venir à la conclusion que cette issue est attribuable à l'utilisation de gentamicine, plutôt qu'à d'autres facteurs, demeure discutable.

Objectifs : L'objectif principal de cette étude était de déterminer si quelque nouveau-né (exposé *in utero* à de la gentamicine intraveineuse et né entre janvier 2002 et avril 2006 au *Victoria General Hospital*) que ce soit présentait des déficits audiolologiques dans le cadre d'une épreuve auditive habituelle. Une telle épreuve est universellement offerte depuis la fin 2001. Nos objectifs secondaires étaient d'examiner les tendances quant au recours à la gentamicine (y compris l'indication, la posologie, la durée) et de déterminer si les taux sériques de gentamicine avaient ou non fait l'objet d'un suivi.

Méthodes : Les femmes à qui l'on avait administré de la gentamicine ont été identifiées au moyen des dossiers pharmaceutiques et leurs dossiers médicaux ont fait l'objet d'un examen afin d'y repérer les facteurs (dont l'abus d'alcool ou d'autres drogues,

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l'administration d'autres médicaments potentiellement ototoxiques, une prédisposition génétique et des infections intra-utérines) qui auraient pu contribuer à la surdité fœtale. Nous avons analysé les résultats de l'épreuve audiologique et les dossiers médicaux des nouveau-nés afin d'y relever les facteurs confusionnels potentiels, dont la prématurité, l'insuffisance de poids à la naissance, de faibles indices d'Appgar, l'anoxie, l'hyperbilirubinémie, la sepsie et la méningite.

Résultats : Des cinquante-trois dossiers analysés, 40 documentaient des naissances vivantes. Aucun cas de perte auditive n'était documenté. Des huit décès fœtaux, six (11,5 %) impliquaient des naissances prématurées avant la viabilité et deux étaient attribuables à une interruption volontaire de grossesse. La pyélonéphrite constituait la principale indication du recours à la gentamicine (48 %), suivie de la chorioamnionite (31 %) et de diverses autres indications (21 %). Une posologie de type 3 f.p.j. a été utilisée pour une durée moyenne de $2,7 \pm 2,3$ jours, ce qui a donné lieu à une dose cumulative moyenne de 764 ± 600 mg de gentamicine. L'âge gestationnel moyen au moment de l'exposition était de 28 semaines. Des taux sériques maternels de gentamicine ont été mesurés dans 72,5 % des cas; de plus, aucune concentration minimale ne se situait au-delà de 2 mg/l. D'autres médicaments potentiellement ototoxiques ont été administrés à la mère dans 17,5 % des grossesses, ainsi qu'à 17,5 % des nouveau-nés immédiatement après la naissance. À l'exception d'un nouveau-né qui est décédé avant que l'on ne puisse procéder à des tests supplémentaires, tous les nouveau-nés ont réussi leurs épreuves audiologiques (dont 89 % dès le dépistage initial).

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INTRODUCTION

The incidence of acute pyelonephritis or chorioamnionitis in pregnancy is 1% to 2%.¹ Untreated pyelonephritis can result in anemia, septicemia, renal dysfunction, pulmonary insufficiency, prematurity, and premature rupture of membranes.^{1,2} Chorioamnionitis may lead to maternal endometritis and coagulopathies and fetal demise or prematurity.³ Between 5% and 10% of babies will have bacteremia or pneumonia.⁴ The predominant pathogen in both maternal infections is *E. Coli*.¹ Gentamicin is a mainstay in the eradication of *E. Coli*,⁵ and conventional dosing (1.0–1.5 mg/kg/dose intravenously every 8 hours) is used in approximately 17 pregnancies annually at Victoria General Hospital (VGH).

In 2003, Schering Pharmaceuticals amended the Garamycin Injectable (gentamicin) product monograph in the Compendium of Pharmaceuticals and Specialties (CPS) to state that gentamicin "may cause fetal harm when administered to pregnant women. There have been reports of total irreversible bilateral congenital deafness."⁶ In response to our enquiry, a company representative stated the monograph change was prompted by 10 case reports of auditory toxicity in exposed babies in Canada over a 30-year period. A search of English language articles published in Medline (1960–April 2006), Embase (1980–April 2006), and PubMed databases (1950–April 2006) using the key words "gentamicin," "ototoxicity," "hearing impairment," "deafness," "fetal" and "neonate" yielded no case reports of

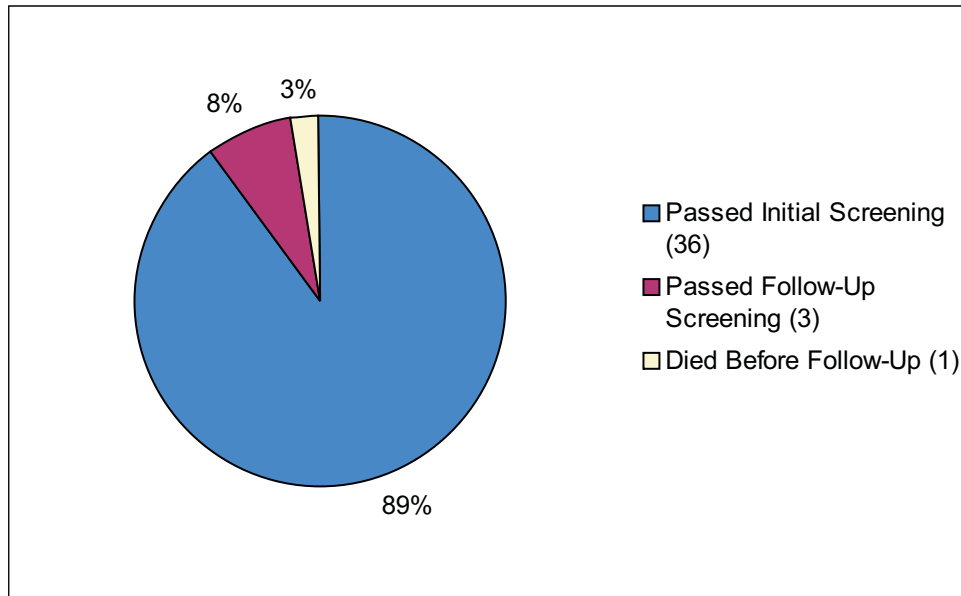
auditory toxicity. The Teris, Reprotox, and Shepards (Micromedex) databases advised caution regarding the use of gentamicin in pregnancy but made no references to adverse audiological outcomes.⁷ The Hungarian Case-Control Surveillance of Congenital Abnormalities found no increase in either congenital abnormalities or teratogenicity due to fetal exposure to gentamicin or neomycin.⁸ Only one case of congenital deafness in an infant born to a mother treated with gentamicin 80 mg three times daily for two days and 100 mg three times daily for one day was identified through the Canadian Adverse Drug Reaction Monitoring Program database.⁹ A single case in Spain was reported in the Spanish literature.¹⁰

Since January 2002, Vancouver Island Health Authority has screened all infants born at VGH for hearing impairment. Babies are initially evaluated with an otoacoustic emission (OAE) test conducted by placing a probe in the baby's ear canal to measure inaudible sounds produced by cochlear vibrations stimulated by audible sound. This detects hearing losses between 2000 and 5000 Hz.¹¹

Humans can hear sounds with frequencies between 20 and 20 000 Hz,¹² but the 500 to 4000 Hz range is most important for speech discrimination.¹³ Gentamicin-induced ototoxicity in adults is progressive from high to low frequency (20 000–9000 Hz),¹⁴ generally bilateral, and potentially reversible.¹⁵ Both OAE and automated auditory brainstem response (AABR) testing have been validated in children and infants to monitor cochlear function after aminoglycoside therapy.^{16–18} Stavroulaki et al. demonstrated that OAE testing in children exposed to more than seven days of gentamicin therapy shows deficits in hearing in the range tested for speech, from 1000 Hz to 5000 Hz. When these children were compared with unexposed controls, a significant difference was seen for each of five frequencies tested.¹⁶ Because of the detectable difference in the range that is usually used for newborn hearing screening tests, we reasoned that by correlating the OAE screening results with mother's use of gentamicin we could detect subtle drug-induced hearing deficits.

At VGH, hearing screenings are usually completed in the first three days of life in the general infant population and near discharge in neonatal intensive care unit (NICU) graduates. Copies of test results are placed with the infants' charts. The estimated number of hearing impairment cases detected within Vancouver Island Health Authority (VIHA) South Island Region is 3 to 6 per 1000 uncomplicated births and 6.8 to 13 per 1000 in infants discharged from NICUs.^{19–21} Other than exposure to ototoxic medications such as furosemide, indomethacin, zidovudine, and ibuprofen, hearing loss may result from genetic causes, intrauterine infections (rubella, cytomegalovirus, herpes

Figure 1. Primary Outcome-Audiology Results



simplex virus, syphilis, toxoplasmosis, varicella), and exposure to teratogens (alcohol, cocaine, methyl mercury, thalidomide, and methamphetamine). Craniofacial abnormalities, prematurity, anoxia, hyperbilirubinemia, bacterial infections (sepsis, meningitis, and otitis media), mumps, low Apgar scores, and low birth weight are also associated with hearing deficits.^{15,19,20,22}

The primary objective of this study was to determine whether any infant exposed in utero to gentamicin between January 2002 and January 2006 demonstrated audiologic deficits on routine hearing screening.

Secondary objectives were to determine the indications for mothers on the antepartum unit at VGH to receive gentamicin and the outcomes of pregnancy. If a live birth occurred, information about the following was collected: the mean dose and duration of gentamicin therapy, concurrent use of other potentially ototoxic medications during pregnancy and the postpartum period, serum trough levels of gentamicin (when obtained), the mean gestational age of fetus at the time of exposure and at delivery, and neonates requiring NICU admission.

METHODS

The project was a single-centre study of all women admitted to the antepartum unit at VGH between January 2002 and January 2006 who received at least one dose of intravenous gentamicin. Pregnancies not resulting in live births were excluded from portions of the data analysis.

The project was approved by the Vancouver Island Health Authority Research Review and Ethical Approval Committee. Some of the mothers had moved since delivery and we were not able to contact them to obtain consent to review their records. The Ethics Committee advised that ethical approval for the study would be given if we obtained a proxy consent by explaining the purpose of the study to a comparable group of mothers. This group was composed of mothers of babies who were currently in the NICU and mothers in a post-discharge parent-child group that met in a community centre close to the hospital. The study was explained to these mothers and their proxy consent to examine records was requested and subsequently obtained.

Pharmacy prescription databases were searched to identify patients who received gentamicin while on the antepartum unit at VGH between January 2002 and January 2006.

Three frequencies are tested using OAE at VGH: 2000, 3000, and 4000 Hz. It has been shown that this technique can measure early subtle outer hair cell damage in the cochlea.¹⁶ An auditory brainstem response test (ABR) that involves placing electrodes on a baby's head to detect brainstem activity in response to a click stimulus (range of 2000–4000 Hz)^{17–19} serves to further assess babies in the NICU and any other babies with questionable results from the first OAE test. In cases where infants are referred for testing in addition to the screenings, a full ABR test ranging from 500 to 4000 Hz is conducted, with recommendations

Characteristics of gentamicin use

Mean dose of gentamicin \pm SD	764 \pm 600 mg
Mean duration of gentamicin therapy \pm SD	2.7 \pm 2.3 days
Mean gestational age at exposure SD	28 \pm 6 weeks
Mothers who received concomitant potentially ototoxic medication	17.5% (n = 7)
Gentamicin serum levels obtained	72.5% (n = 29)
Mean gestational age at birth \pm SD	36 \pm 4 weeks
NICU admission required	30% (n = 12)
Neonates who received concomitant potentially ototoxic medication	17.5% (n = 7)

SD: standard deviation; NICU: neonatal intensive care unit.

for additional genetic testing and consultation with ear, nose, and throat specialists as required.

Charts were reviewed for audiology test results and for potential confounding factors such as family history, premature birth, low birth weight, complications of delivery reflected by low Apgar scores or low umbilical cord artery pH, and exposure to teratogens or potentially ototoxic medications other than gentamicin both in utero and during the neonatal period.

RESULTS

Of the 40 infants exposed to gentamicin in utero on the VGH antepartum unit between January 2002 and January 2006 whose charts were assessed, none demonstrated audiologic deficits on routine hearing screening (Figure 1).

Gentamicin was used in 28 pregnancies (48%) for pyelonephritis, in 16 (31%) for chorioamnionitis, and in 11 (21%) for other indications. The mean (\pm standard deviation) dose of gentamicin was 764 \pm 600 mg for a duration of 2.7 \pm 2.3 days (Table). Mean gestational age at exposure was 28 \pm 6 weeks. Gentamicin blood levels were monitored in 72.5% of women and no serum trough level was greater than 2 mg/L (Figure 2).

DISCUSSION

Three infants (8%) did not pass initial OAE and ABR hearing screenings but went on to complete follow-up screening successfully at a community audiology clinic. This is comparable with the baseline percentage of infants screened at VGH (7%) who will require outpatient follow-up. All three cases involved other confounding factors for hearing loss.

Infant No. 1 was born at 27 weeks' gestation and received gentamicin 2.3 mg intravenously (IV) at 24-hour intervals for six doses. The mother of infant No. 1 also received additional potentially ototoxic medication (indomethacin 100

mg rectally, then indomethacin 25 mg orally for four doses at 23 weeks' gestation).

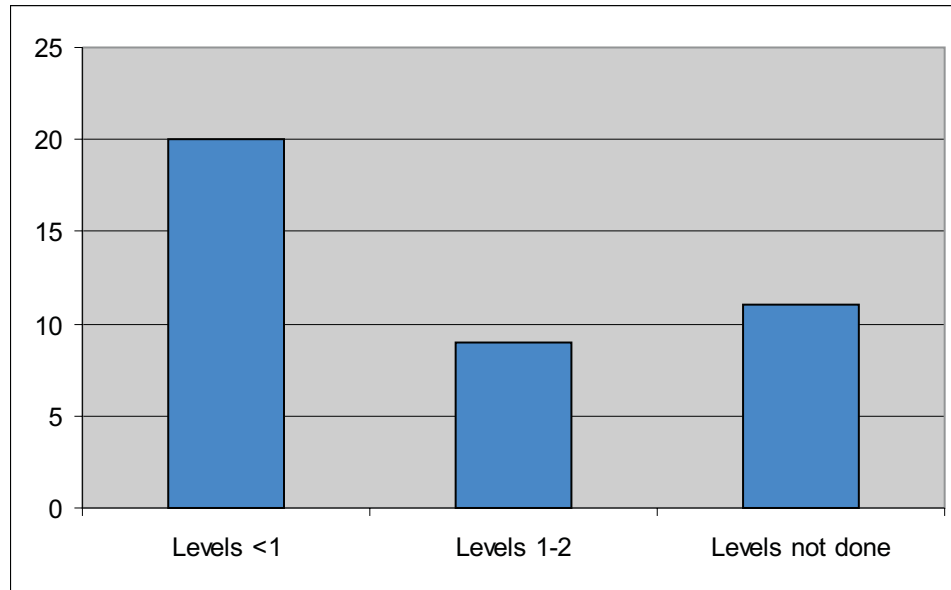
Infant No. 2 was born at 26 weeks and 6 days of pregnancy and received gentamicin 3.2 mg IV at 48 hour intervals for five doses and furosemide 2 mg IV for two doses.

Infant No. 3 was born at 38 weeks' gestation and was otherwise healthy. This infant's mother had received three separate courses of gentamicin in the 20th, 34th, and 38th weeks of gestation for a total exposure of 2700 mg over 10.3 days.

Congenital hearing problems are rare, and consequently a very large sample size would be needed to prove beyond a reasonable doubt that in utero gentamicin does not increase the risk of ototoxicity. In order to show an increase in hearing deficits due to gentamicin exposure in utero from the North American average of 5 in 1000 births to 7 in 1000 births with an 80% power and an alpha of 0.05, it would be necessary to study 11 629 gentamicin exposures. Assuming gentamicin is used in 0.005% of Canadian pregnancies (as is current VGH practice) and that Canada's birth rate remains constant at about 340 000 births annually, this would take approximately seven years. As only 77% (40 of 52) of the pregnancies involving gentamicin administration at VGH result in live births, the duration further increases to about nine years.

This also assumes that screening for hearing loss is universally available. In fact, VIHA is currently one of the few health authorities to offer the service; many other health authorities offer screening only for "at risk" neonates.

The results of this study are similar to other reports relating use of gentamicin in pregnancy to audiologic outcomes in newborns. Locksmith et al.⁴ studied two groups of expectant mothers with chorioamnionitis who were treated with either conventional low-dose gentamicin (120 mg IV loading dose followed by 80 mg IV three times daily), or high-dose once daily therapy (5.1 mg/kg once daily). Only one dose was given prior to delivery in all but one subject. Maternal serum gentamicin levels 30 minutes after

Figure 2. Maternal Serum Gentamicin Trough Levels

gentamicin infusion and at delivery were obtained. Umbilical cord blood levels at delivery were also measured. Cord blood levels in babies exposed to the high-dose regimen were therapeutic at approximately 40% of maternal levels. In the conventional dose group, the cord blood level also approximated 40% of maternal levels, but because of the lower maternal concentration was below the therapeutic range. Audiologic findings are similar to those of our study; all infants passed initial hearing screenings except one, who passed on follow-up testing. Ototoxic potential of once daily versus conventionally dosed gentamicin remains a controversial topic. A definitive answer to this question would require a higher number of mother–baby pairs than could realistically be obtained at any single institution in an appropriate time frame.⁴

A study in guinea pigs suggests that concurrent treatment of gentamicin-exposed mothers with L-carnitine may protect against pro-apoptotic effects of gentamicin and subsequent damage to auditory hair cells.²³ Perhaps in the future L-carnitine will be given routinely in combination with gentamicin.

Although it is impossible to prove beyond a reasonable doubt that gentamicin in pregnancy is not ototoxic, the available results are reassuring. Pregnancies requiring gentamicin are by nature complicated; 11.5% (6 of 52) of pregnancies in this study resulted in fetal demise. Gentamicin is a useful antibiotic in obstetrics because of its excellent coverage of *E. Coli* and other gram-negative

organisms, its activity against MRSA,⁶ and its relative lack of allergic cross-reactivity. A generic form is widely available, reasonably priced, and relatively simple to administer in a hospital setting. In pregnant women, the renal perfusion is brisk, and, barring the use of repeated doses over a prolonged period of time, toxicity is seldom encountered. In this small series of patients, there were no cases of auditory toxicity in newborns exposed to gentamicin in utero in conventional three times daily (1–1.5 mg/kg) dosing, although the sample size does not reach statistical significance.

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