

Title: Pharmacodynamic Analysis of Hearing Impaired Neonates Treated with Amikacin.

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Objectives: To investigate amikacin risk factors for hearing loss in neonates treated with amikacin.

Methods: A clinical audit was undertaken to review hearing tests done within 3 – 6 months of discharge on neonates who had received amikacin in NICU at Dunedin Hospital from 1st Oct 2003 to 31st Jan 2007. Those neonates tested were considered at risk of hearing impairment due to prematurity, low birth weight, jaundice or use of aminoglycosides. The most common form of hearing screening tests involved the use of otoacoustic emission testing. This was tested by measuring either distortion product otoacoustic emissions or transiently evoked otoacoustic emissions (TEOAE). The auditory brain stem response test method was also used when indicated. The PD analysis involved modelling the data obtained from the hearing screen audit (n = 36) and determining if the drug concentrations could be correlated with a specific outcome measure related to the effect of hearing loss. To undertake the PD analysis, the posthoc estimates from a PK model and clinical data from the audit were included in a logistic regression model using Stata®, version 8.

Results: Seven of the neonates within the audit were reported to have partial to total hearing impairment in one or both ears at the time of testing. The remaining neonates (n = 29) elicited repeatable TEOAE responses for both ears, which was consistent with hearing thresholds of better than 25 dBHL across the frequency range. This result represented a pass in the hearing screening test and indicated sufficient cochlear hearing acuity for the development of normal speech and language skills. The mean \pm SD for current weight (kg) was 1.3 ± 0.57 , gestational age (GA) (weeks) 28 ± 3.21 and postnatal age (days) 12.7 ± 11.02 . The maximum amikacin peak during treatment had a median (range) of 30.3 (17.3 - 59.7) mg/L. The total number of days that infants received amikacin treatment from all episodes of treatment had a median (range) of 4 (1 – 34) days. The independent variables associated with hearing impairment included receiving vancomycin treatment, a high C-reactive protein (CRPM) during treatment, lower gestational age and a greater number of days treatment with amikacin or aminoglycosides (including gentamicin). The statistically significant parameters were then used in a backward and forward stepwise logistic regression model. The most effective predictor of hearing impairment was vancomycin treatment, GA (weeks) and CRPM (mg/L) during treatment, with a χ^2 of 0.0006 and R^2 of 0.495 for the model (Table 1).

Table 1: Backward stepwise logistic regression

Description	n	Odds Ratio	SE	95% CI	χ^2	R^2
Vancomycin treatment	35	12.311	16.47	0.893-169.62	0.0006	0.495
GA (weeks)	35	0.549	0.163	0.306-0.985		
CRPM (mg/L) during treatment	35	1.022	0.012	0.998-1.047		

Conclusions: This logistic regression model explained almost 50 % of the variability associated with independent variables related to the effect of hearing impairment. Risk factors for hearing loss in neonates treated with amikacin are co-medication with vancomycin, lower gestational age and elevated C-reactive protein.