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Pharmacodynamic Analysis of Hearing Impairment in Neonates Treated with Amikacin

Introduction

- Ototoxicity can be associated with either cochlear or vestibular effects, depending on the specific aminoglycosides.
- Ototoxicity results from damage to type 1 vestibular sensory cells and outer hair cells of the basal cochlear in turn, resulting in high-frequency hearing loss and subsequently to low frequency hearing loss with increasing toxicity.
- Minimum (trough) concentrations of amikacin are often too high to be considered safe and may induce ototoxicity.
- Risk factors associated with hearing impairment in neonates include prematurity/birth weight <1.5 kg, severe birth asphyxia, congenital perinatal infection, aminoglycoside therapy and co-medication with renal excreted drugs.
- The overall incidence of hearing impairment in neonates is reported to be approximately 4-5%.

Objectives

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

Methodology

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 1 Oct 2003 to 31 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 used 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.

A population PK analysis included all the study subjects and was performed using NONMEM, version 5. A one-compartment first order elimination model was utilised. The final covariate model estimated clearance (CL) = 0.23 • 0.0746 •• (PMA) • 0.691 •• (CWT) and volume of distribution (V) = 0.957 • 0.89 •• (CWT).

To undertake the PD analysis, posthoc estimates of AUC, C_{max} from a PK model and clinical data from the audit were included in a logistic regression model using Stata®, version 8. The outcome measure was hearing impairment.

Results

Table 1 Summary characteristics from the hearing screen audit

Characteristics of patients	Hearing impaired (n = 7, 19.4%) Mean ± SD n (%)	No hearing impairment (n = 29, 80.5%) Mean ± SD n (%)	All patients (n = 36) Mean ± SD n (%)
Sex (male)	2 (28.5 %)	19 (65.5 %)	21 (58.3 %)
Late onset sepsis	5 (71.4 %)	8 (27.5 %)	13 (36.1 %)
Treatment failure	2 (28.5 %)	1 (3.4 %)	3 (8.3 %)
GA (weeks)	26.0 ± 3.4	28.5 ± 3.0	28.0 ± 3.2
PNA (days)	15.7 ± 21.3	11.9 ± 7.1	12.7 ± 11.0
BWT (kg)	0.90 ± 0.4	1.2 ± 0.3	1.1 ± 0.3
CWT (kg)	1.2 ± 1.0	1.3 ± 0.4	1.3 ± 0.5
CRPM (mg/L)	74.9 ± 91.5	17.8 ± 28.3	29.2 ± 51.5
APG1	4.9 ± 2.7	6.4 ± 2.1	6.1 ± 2.3
APG2	8.3 ± 2.8	8.9 ± 1.3	8.8 ± 1.6
Gentamicin treatment	7 (100 %)	24 (82.7 %)	31 (86.1 %)
Vancomycin treatment	4 (57.1 %)	2 (6.8 %)	6 (16.6 %)

Table 2 Univariate logistic regression of hearing impairment

Description of logistic regression	n	Odds Ratio	SE	95 % CI	p-value
Vancomycin treatment	36	18	19.05	2.26 - 143.30	0.004*
CRPM (mg/L) during treatment	36	1.01	0.01	1.0 - 1.039	0.015*
Total duration of treatment with	36	1.11	0.054	1.009 - 1.221	0.021*
Total duration of treatment with	36	1.1	0.053	1.00 - 1.21	0.024*
GA (weeks)	36	0.673	0.139	0.448 - 1.01	0.029*
Confirmed sepsis	36	6.56	6.13	1.051 - 40.94	0.033*
No. of treatment episodes (septic and Total duration of treatment during septic episodes (days)	36	2.05	0.711	1.04 - 4.04	0.033*
episodes (days)	36	1.14	0.076	1.00 - 1.300	0.041*

Note: *Statistically significant (p<0.05)

Table 3 Backward stepwise logistic regression of risk factors for hearing loss in neonates treated with amikacin

Description	n	Odds Ratio	SE	95 % CI
Vancomycin treatment	35	12.31	16.4	0.89 - 169.62
GA (weeks)	35	0.54	0.16	0.30 - 0.98
CRPM (mg/L) during treatment	35	1.02	0.01	0.99 - 1.04

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.

For all patients the mean ±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 (Table 1).

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, duration of treatment and a greater number of days treatment with amikacin or aminoglycosides (including gentamicin) (Table 2).

The statistically significant parameters on univariate analysis 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 p-value of 0.0006 and R² of 0.495 for the model (Table 3).

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.

Future directions

- Further investigate amikacin induced ototoxicity in neonates.
- Development and implementation of optimal amikacin dosing regimen for neonates.