Effect of Successive Gentamicin and Amikacin Therapies on Renal Function of Neonates

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Abstract

Gentamicin and amikacin are aminoglycoside antibiotics which are renally excreted and known to cause nephrotoxicity. Neonatal eGFR per body surface area is lower than in adults and exposure to nephrotoxic drugs could lead to more suppression in kidney function. The aim of this study was to investigate the effect of administering successive courses of gentamicin (first-line) and amikacin (second-line) therapy on neonatal kidney function. Data were collected from patient records of neonates receiving gentamicin (July-December 2019) and amikacin (July-December 2020) at the Neonatal Unit of Windhoek Central Hospital (Namibia). 44 neonates on gentamicin and 35 on amikacin were included in this study. Aminoglycoside dose was administered as a slow intravenous bolus and two blood samples taken for pharmacokinetic analysis. Other information collected: gestational age, postnatal age (PNA), weight, height, serum creatinine, and dosage regimen. Primary outcomes were correlation of eGFR with PNA, and the time it took to clear the drug to $< 1 \mu\text{g/mL}$; eGFR was calculated using the Schwartz method. The negative correlation between eGFR and PNA was significant ($r = -0.370$, $p = 0.034$). Therapeutic range C_{max} were achieved in 27.3% gentamicin neonates (15–25 $\mu\text{g/mL}$), and 17.1% in amikacin (55–65 $\mu\text{g/mL}$). Proportion of neonates with a $C_{\text{min}} < 1 \mu\text{g/mL}$ within the 24-hour dosage interval were 72.7% and 82.9% for gentamicin and amikacin, respectively. *Conclusion:* The decline in kidney function for neonates while on amikacin was significant. However, a considerably high proportion of amikacin neonates (82.9%) were able to clear the drug to $< 1 \mu\text{g/mL}$ within 24 hours.

What Is Known

- Gentamicin and amikacin are aminoglycoside antibiotics which are renally excreted and known to cause nephrotoxicity.
- Neonatal eGFR per body surface area is lower than in adults and exposure to nephrotoxic drugs could lead to further suppression in kidney function.

WHAT IS NEW

- The results from this study show that successive use of gentamicin and amikacin as first-line and second-line therapies, respectively, leads to suppression of kidney function in the neonate.
- Although nephrotoxicity may result from the successive use of gentamicin and amikacin, the majority of neonates are still able to clear the drug to concentrations below the toxicity threshold before the next dose.

Introduction

Gentamicin and amikacin are aminoglycoside antibiotics that have a rapid bactericidal action and are primarily used against nosocomial septic infections due to aerobic gram-negative bacteria [1]. However,

the use of these potent broad-spectrum antimicrobials is limited by the associated drug-induced adverse effects, namely, nephrotoxicity and ototoxicity which result from accumulation and retention of the drug in the proximal tubular cells of the kidneys, and the labyrinth of the ear, respectively [1,2]. Over 90% of the aminoglycoside dose is eliminated by excretion through the kidneys with urine concentrations attaining 50-200 µg/mL [1,3]. Nephrotoxicity due to aminoglycosides correlates with total dose and duration of therapy and is known to result in reversible mild renal impairment in 8-26% of patients characterized by a rise in serum creatinine concentrations; the condition is reversible because proximal tubular cells have the capacity to regenerate [4,5]. The World Health Organization (WHO) recommends gentamicin in combination with ampicillin or penicillin as first-line therapy against neonatal sepsis for synergy and because of low reported resistance patterns to gentamicin [6–8]. Therapeutic drug monitoring (TDM) is used to limit the occurrence of toxicity in neonates undergoing aminoglycoside therapy [6,7]. For once-daily dosing, trough concentrations for gentamicin are recommended to be <1 µg/mL and 15-25 µg/mL for peak concentrations, while for amikacin the troughs should be <1 µg/mL and 55-65 µg/mL for peak concentrations [11,12]. In neonates, the pharmacokinetic approach to dosage adjustment is preferred than the high-dose extended interval method [1,11,13–15]. Although the nephrotoxic effect of gentamicin and amikacin in neonates is well documented, studies involving neonates receiving gentamicin as first-line followed by amikacin as second-line therapy to report on the effect on renal function are lacking. The purpose of this study is to report on the impact in kidney function of neonates who were receiving gentamicin and amikacin as first- and second-line therapy, respectively, in the Neonatal Unit based at Windhoek Central Hospital, Namibia. In this facility, gentamicin is prescribed as first-line prophylactic therapy against sepsis and amikacin is only given as second-line if there is no improvement in the symptoms.

Materials And Methods

Study setting and patient population

This was a retrospective cross-sectional quantitative study conducted at the Neonatal Unit of the Maternity ward at the Windhoek Central Hospital in Windhoek, Namibia. The data were derived from two population pharmacokinetic studies in which one set of neonates were receiving gentamicin and the other were receiving amikacin in the same neonatal unit using the same methodology. Data for gentamicin were collected from 44 neonates starting from 4 July 2019 to 29 December 2019, while data for amikacin were collected from 35 neonates from 25 July 2020 to 7 December 2020 (all data were collected over a total period of 1 year). The patients who were receiving gentamicin were not the same patients as those on amikacin. Patients who were included in the study were those who had two reported drug concentrations, and at least one serum creatinine measurement.

Study Procedure

Aminoglycoside therapy was prescribed against either suspected or confirmed sepsis. Gentamicin in combination with a penicillin such as penicillin G or ampicillin was indicated as first-line in prophylaxis

against suspected neonatal sepsis where there are risk factors such as premature birth, very low (and extremely low) birthweight (VLBW and ELBW), and respiratory distress syndrome (RDS). Amikacin was given in combination with piperacillin/tazobactam as second-line therapy if signs of sepsis persisted even after the gentamicin course had been completed.

Gentamicin therapy was initiated soon after birth, while treatment with amikacin was only initiated around day 5 when the gentamicin course had been completed with no improvement in the patient's condition. All neonates who received amikacin had first been treated with gentamicin as first-line.

Aminoglycoside dose was administered by the ward nurses as a slow intravenous bolus injection via a cannula and two blood samples were withdrawn by venipuncture thereafter. Each one sample was taken at a time falling in either of the following sampling blocks: 4-6 minutes (0.06-0.10 h), 6-180 minutes (0.1-3.0 h), or 180-320 minutes (3-5.4 h). Blood samples were collected into sterile 500 µL serum separating tubes (SST), centrifuged and serum stored in Eppendorf tubes at -20 °C to await analysis.

Laboratory methods

Serum creatinine concentration measurements were done by the enzymatic method using the Cobas® 6000 analyzer (Roche Diagnostics, IN, USA). Gentamicin and amikacin concentrations were measured using the Indiko Plus™ autoanalyzer (Thermo Fisher Scientific Inc, CA, USA). The lower limit of quantifications for gentamicin and amikacin were stated given by the manufacturer as 0.3 µg/mL and 0.8 µg/mL, respectively.

Data analysis

The two reported drug concentrations were plotted onto semi-logarithmic graph paper to estimate the half-life, C_{max} , and the time to reach the target trough concentration which was <1 µg/mL for both gentamicin and amikacin. The eGFR was estimated by using the Schwartz method for estimating creatinine clearance in paediatrics (equation 1):

$$eGRF(\text{in mL/min/1.73 m}^2) = \frac{\text{Factor} \times \text{Height (in cm)}}{\text{Serum creatinine (in mg/dL)}} \quad \{1\}$$

where: Factor is 0.43 in term neonates or 0.33 in preterm neonates.

The results were summarized using descriptive statistics such as median, range, and percentages. A two-tailed unpaired t-test was used in Excel (Microsoft Excel, Redmond, WA, USA) to compare means. A $p < 0.05$ was taken to be the critical value for statistical significance.

Research ethics

The study was approved by the University of Namibia Human Research Ethics Committee and the Research Committee of the Ministry of Health & Social Services in Namibia. Informed consent was first

sought and obtained from the mothers of the newborns before they were included in this study.

Results

Of the 44 neonates on gentamicin and 35 who received amikacin, 81.8% and 68.6% were of premature birth, respectively. The two groups of neonates had demographics with no statistical difference: gestational age (GA) ($p=0.979$), height ($p=0.510$), and birth weight ($p=0.213$) (Table 1). Although the p -values were close to significance, there was no statistical difference in the eGFR between the two cohorts ($p=0.060$), or when only the preterm babies from the cohorts were compared ($p=0.068$). Gentamicin (5 mg/kg) and amikacin (15 mg/kg) were given for a duration of 5 and 7 days, respectively (Table 1). Gentamicin was initiated at a mean PNA of 3 days (range: 1-14 days), and amikacin at 12 days (range: 5-25 days). Neonates with C_{max} concentrations falling within the therapeutic range were 27.3% in gentamicin and 17.1% in amikacin. Target peak concentrations (C_{max}) were better achieved in gentamicin than in amikacin (Table 2). 72.7% and 82.9% were able to reach the toxicity threshold (or target trough) of $<1 \mu\text{g/mL}$ within 24 hours for gentamicin and amikacin, respectively (figure 1). Correlation of eGFR with GA was positive and significant for both gentamicin ($p=0.005$) and amikacin ($p=0.003$), while correlation between eGFR and PNA was positive but not significant for gentamicin ($p=0.077$), but negative and significant in the case of amikacin ($p=0.034$) (see Figure 2). 6 out of 43 (14.0%) of babies on gentamicin died while still receiving gentamicin therapy, and 3 out 26 (11.5%) died during amikacin therapy.

Discussion

Gentamicin and amikacin are efficacious antibiotics that are useful in the management of infectious diseases, but they are also known to be associated with two serious adverse reactions, namely: ototoxicity and nephrotoxicity [1]. The effects on neonatal renal function due to successive use of these two aminoglycosides as first- and second-line therapy in a clinical setting have not been reported. It is suspected that prolonged exposure to these drugs could lead to nephrotoxicity. Studying the impact of the current successive use of gentamicin and amikacin on the kidney function of newborns will inform appropriate dosage regimen design which will ensure safety by minimizing nephrotoxicity.

In this study, concentrations of gentamicin and amikacin in serum were measured and their pharmacokinetics determined. Serum creatinine concentrations were used to calculate eGFR values which were then correlated with both neonatal GA and PNA. In this study, both gentamicin and amikacin eGFR had a significant positive correlation with GA. This is expected since neonates born with a higher GA will have a more advanced renal histological development than those born earlier on [16]. In addition, neonates on amikacin had more developed renal capacity going into their second or third week of life and therefore were able to clear the drug to safe levels before the next dose in virtually all cases. This is the same reason why eGFR was higher in amikacin than in gentamicin. A study of 91 neonates receiving 5-6 mg/kg/day of gentamicin reports that 63% had potentially toxic trough concentrations ($>2 \mu\text{g/mL}$) of whom most were premature with lower gestational age, low birthweight, and in their first week of life [17]. When eGFR is correlated with PNA, eGFR significantly declined while neonates were receiving amikacin.

Initiation of gentamicin was as early as day 1 after birth and therapy lasted for 5 days, after which amikacin therapy was administered. Kidney function was in decline (already) from the onset of amikacin therapy (day 5 after birth). The decline of renal function with increasing neonatal chronological age observed in amikacin could be due to the successive exposure of the newborns to the two aminoglycosides which resulted in nephrotoxicity, but it appears kidney damage had already set in within the first 5 days of gentamicin therapy. Achievement of recommended C_{max} values for both gentamicin and amikacin was not high (27.3% and 17.1%, respectively) and large proportions of patients had concentrations that were supratherapeutic (31.8% for gentamicin and 51.4% for amikacin). Increasing the mg/kg dose across the board might result in more patients with concentrations in the therapeutic range but will also lead to many more neonates with supratherapeutic concentrations and even worse nephrotoxicity. The best solution would be to individualize the dose according to each patient's pharmacokinetic parameters using equation 2:

$$Dose = target\ C_{max} \times CL \times \tau \quad \{2\}$$

where CL is the drug clearance, and τ is the dosing interval. Over 90% of the aminoglycoside dose is eliminated by excretion through the kidneys with urine concentrations attaining 50-200 $\mu\text{g/mL}$ [1,3,18]. Several factors are known to affect renal function in neonates leading to altered drug exposure and response, namely: kidney development/maturation, underlying kidney diseases/comorbidities, medications, and environmental (and genetic) factors [19]. Nephrogenesis begins and concludes between weeks 5-35 of gestation followed by improved intrarenal blood flow after birth, but renal function in the neonate is still much lower in comparison to that of adults because of the following factors: immature glomerular filtration and tubular secretory mechanisms, reduced renal perfusion pressure, and insufficient osmotic load to produce full counter-current effects [19]. Because preterm neonates are born at <37 weeks of gestation while nephrogenesis is still incomplete their capacity for renal excretion/elimination of drugs is the most affected [20]. A comparison between neonates born small for gestational age and preterm neonates with appropriate weight for gestational age showed that neonates with a lower body weight also have a reduced renal function [21]. Although it is difficult to ascertain the association of gentamicin and toxicity in neonates as poor feeding, asphyxia and sepsis are reported to also cause acute kidney injury [22–24], studies have shown that gentamicin and amikacin are potentially nephrotoxic and are known to cause acute kidney injury in neonates leading to impaired renal function [25,26]. A study by Darmstadt et al (2008) reports that the risk of toxicity due to gentamicin is increased by repeat courses, persistent exposure to trough concentrations above 2 $\mu\text{g/mL}$ for more than 10 days and renal impairment as a pre-existing condition [27]. Impaired renal function results in decreased GFR which has a direct effect on the clearance of drugs that are eliminated primarily by glomerular filtration [28–30]. This leads to higher plasma concentrations, prolonged half-life and increased exposure to such drugs [19].

This study has shown that successive exposure of neonates to gentamicin and amikacin as first- and second-line therapy, respectively, leads to nephrotoxicity as demonstrated by the significant decline in

eGFR with increasing PNA while patients are on second-line therapy. Nephrotoxicity seems to have set in during gentamicin therapy as it is already observable from the onset of amikacin treatment. However, the proportions of patients who were able to clear the drug to reach the toxicity threshold of $<1 \mu\text{g/mL}$ within the dosage interval of 24 hours were considerably high (72.7% for gentamicin, and 82.9% for amikacin). To improve efficacy and safety of gentamicin and amikacin in newborns, eGFR should be monitored and the dose can be adjusted using the pharmacokinetic approach.

A limitation of the study is that the eGFR values during gentamicin and amikacin therapy were obtained in two different cohorts of neonates. However, the demographic characteristics of the two cohorts of neonates were similar strongly suggesting that the reduction in kidney function in the neonates on amikacin therapy was the result of the successive treatment with two aminoglycosides.

Abbreviations

C_{max} – maximum serum drug concentrations

C_{min} – minimum serum drug concentrations

CL – drug clearance

eGFR – estimate glomerular filtration rate

GA – gestational age

PNA – postnatal age

TDM – therapeutic drug monitoring

Declarations

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Code availability: N/A

Authors' contributions: Bonifasius Siyuka Singu: data collection, analysis, and main author; Milka Ndapandula Ndeunyema: data collection and editing; Ene Ikpong Ette: study supervision and mentorship; Clarissa Hildegard Pieper: study supervision and technical guidance; Roger Karel Verbeeck: main supervisor, review of the final write-up.

Ethics approval: The study was approved by the Human Ethics Committee of the University of Namibia and of the Ministry of Health & Social Services.

Consent to participate: Informed consent was obtained from the mothers of the neonates before inclusion in the study.

Consent for publication: N/A.

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Tables

Table 1 Patient demographics for neonates on gentamicin and amikacin.

		Gentamicin (n=44)	Amikacin (n=35)
Sex	Male	25 (56.8%)	23 (65.7%)
	Female	19 (43.2%)	12 (34.3%)
Status	Preterm	36 (81.8%)	24 (68.6%)
	Term	8 (18.2%)	11 (31.4%)
Gestational age (weeks)	Median (range)	32 (27-40)	32 (24-40)
Postnatal age (days)	Mean (range)	3 (1-14)	12 (5-25)
Birth weight	Median (range), (g)	1573 (895-3920)	1920 (940-4500)
	NBW (≥2500g)	8 (18.2%)	9 (25.7%)
	LBW (<2500g)	19 (43.2%)	14 (40.0%)
	VLBW (<1500g)	15 (34.1)	10 (28.6%)
	ELBW (1000g)	2 (4.5%)	2 (5.7%)
Birth height (cm)	Median (range)	42 (30-53)	41 (28-55)
Body Surface Area (m ²)	Median (range)	0.137 (0.088-0.240)	0.149 (0.088-0.267)
eGFR (mL/min/1.73 m ²)	Median (range)	20.3 (8.7-50.4)	23.2 (10.7-64.9)
Dose (mg)	Median (range)	8.0 (4.5-17.0)	29 (14-62)
Peak concentration or C _{max} (µg/mL)	Median (range)	16 (4-64)	68 (11-260)
Time to reach 1 µg/mL (h)	Median (range)	14.2 (4.3-118.0)	14.6 (5.9-63.3)
Duration of therapy (days)	Median (range)	5 (2-8)	7 (3-12)

Table 2 Proportion of neonates with Peak drug concentrations falling within the recommended ranges.

	Peak concentration ($C_{\max}$)	Proportion of patients
Gentamicin ($n=44$)	Below target range: $<15 \mu\text{g/mL}$	40.9%
	Within target range: $15\text{-}25 \mu\text{g/mL}$	27.3%
	Above target range: $>25 \mu\text{g/mL}$	31.8%
Amikacin ($n=35$)	Below target range: $<55 \mu\text{g/mL}$	31.4%
	Within target range: $55\text{-}65 \mu\text{g/mL}$	17.1%
	Above target range: $>65 \mu\text{g/mL}$	51.4%

Figures

Figure 1

The time it took for aminoglycoside concentrations to reach the recommended trough concentrations, the horizontal line marks 24 hours. (a) gentamicin: $n=43$, trough $<1 \mu\text{g/mL}$), and (b) amikacin: $n=35$, trough $<1 \mu\text{g/mL}$.

Figure 2

Correlation of eGFR with gestational age (a and b) and postnatal age (c and d) in neonates while receiving gentamicin and amikacin. In d) A negative correlation can be observed between eGFR and postnatal age in neonates receiving amikacin.