AMINOGLYCOSIDE TROUGH LEVELS, RENAL FUNCTION AND HEARING ACUITY IN PAEDIATRIC PATIENTS AT KENYATTA NATIONAL HOSPITAL

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U51/87531/2016

A Thesis submitted in partial fulfillment of the requirements for the award of the degree of

Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance.

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DECLARATION OF ORIGINALITY FORM

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Declaration by supervisors:

This thesis has been submitted for research and examination with our approval as University supervisors.

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DEDICATION

This work is fondly dedicated to my daughters Ilhan and Ilham, my husband Mr. Abdiaziz Abdi, a renowned business man and my lovely parents, Dr. Margaret Mulaa, PhD (chief research scientist in Kenya) and Mr. Juma Mulaa Nassor Khalifa (catographer). They have all been supportive and very patient as I took time to pursue career advancement.

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Dear Dr. Mulaa

Re: Approval of Annual Renewal – Evaluation of the effects of aminoglycoside trough levels on the risk of ototoxity among paediatric patients admitted at Kenyatta National Hospital (P697/12/2017)

Refer to your communication dated February 20, 2019.

Upon review of your communication, the KNH-UON ERC hereby grants you annual extension approval for ethics research protocol **P697/12/2017**.

The approval dates are 19th March 2019 – 18th March 2020.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN- ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.

g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

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The Chairperson, KNH-UoN ERC
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ABBREVIATIONS AND ACRONYMS

AKI	Acute Kidney Injury
CT scan	Computerized Axial Tomography
EOS	Early Onset Sepsis
ELBW	Extremely Low Birth Weight
GBS	Group B Streptococcus
GFR	Glomerular Filtration Rate
HSV	Herpes Simplex Virus
IV	Intravenous
LBW	Low Body Weight
LOS	Late Onset Sepsis
MRSA	Methicillin-Resistant *Staphylococcus Aureus*
PCR	Polymerase Chain Reaction
PK	Pharmacokinetic
SNHL	Sensorineural Hearing Loss
TDM	Therapeutic Drug Monitoring
WHO	World Health Organization
UEC	Urea, Electrolyte, and Creatinine
VD	Volume of Distribution

OPERATIONAL DEFINITIONS

Clearance

The rate at which a drug is cleared from the body and it is measured in volume per unit time (ml/min).

Early onset sepsis

An infection occurring within < 3 days of birth; usually presenting with pneumonia or sepsis.

Extremely Low Birth Weight infant

An infant with weight <1000g.

Low Body Weight infant

(LBW infant) are infants with weight 1000 to < 1500g

Neonate

A baby that is 0-30 days of age.

Pharmacokinetics

This is what the body does to the drug. It entails absorption, distribution, metabolism, and excretion.

Preterm neonate

Is a newborn who is less than 37 weeks' gestational age.

Therapeutic range

The range of serum drug concentrations which is not below the minimum effective concentration or above toxic concentrations.

Therapeutic ratio

The ratio between the minimum effective concentration and toxic concentration.

Volume of distribution

The volume required to contain the entire amount of drug in the body at the concentration of the drug in plasma.

Hyponatremia

Serum sodium levels below 135 mmol/L. Hyponatremia is categorized as mild (130-134mmol/L), moderate (125-129mmol/L) and profound <125mmol

Hypokalemia

Serum potassium levels of less than 3.5 mmol/L. It is classified as moderate hypokalemia (2.5-3.0 mmol/L) and severe (<2.5mmol/L)

Normal serum creatinine

Normal serum creatinine for children up to 12 years of age 25-70 mmol /L.

Therapeutic drug monitoring

The clinical practice of measuring specific drugs at designated intervals to maintain a consistent concentration in a patient's bloodstream, thereby optimizing dosage regimen.

ABSTRACT

Background

Aminoglycosides are antibiotics used in pediatrics for the management of severe infections. In resource limited settings, monitoring of drug levels for efficacy and toxicity is minimal and dosing is largely empiric. This may lead to irreversible consequences such as hearing loss and renal toxicity.

Objective

To determine aminoglycoside trough levels, risk of early hearing loss and renal toxicity among pediatric patients at KNH.

Methods

This prospective cohort study was conducted in the pediatric wards of the KNH between May and September, 2018. Patients aged 5 years and below receiving amikacin or gentamicin treatment were included. Renal function and hearing loss screening were determined at baseline and after treatment. Aminoglycoside trough levels were determined on day three before the third dose.

Data on participant demographic characteristics, kidney function, hearing screening, drug serum trough levels were collected. The main outcome variable was aminoglycoside serum trough levels, hearing loss and Acute Kidney Injury (AKI).

Results

The prevalence of aminoglycoside use was 57.12%, 3 (10%) participants on amikacin and 30 (27%) on gentamicin had supra-therapeutic levels of >1 mcg/mL and >2 mcg/mL respectively. The predictors for supra-therapeutic levels were age <18 months (adjusted OR 0.36, 95% CI: 0.14 - 0.92), and weight <10kgs (adjusted OR 0.2, 95% CI: 0.07 - 0.53). The incidence of acute kidney injury (AKI) and hearing loss was 0.136 and 0.007.

Conclusion

There was a high risk of developing Acute Kidney Injury in patients who received aminoglycoside therapy particularly gentamicin. Therefore, there is need to review the existing aminoglycoside use protocols to include routine monitoring of patients on this therapy.

CHAPTER ONE: INTRODUCTION

1.1 Background

Aminoglycosides are a class of antibiotics that are frequently used in pediatrics for the management of severe infections such as neonatal sepsis (1,2) and streptococcal infections (3). They are bactericidal with activity mainly against aerobic gram-negative bacilli and cocci (4,5). Aminoglycosides available in the Kenya essential medicines and in clinical use in Kenya include gentamicin and amikacin. These drugs are used in pediatrics for the management of severe gram-negative infections such as neonatal sepsis and pneumonia (6). They are commonly used as either a single agent or in combination with other antibacterials such as the penicillins (6).

Aminoglycosides have a narrow therapeutic window and therefore the dosing and pharmacokinetics of this class of drugs are important determinants of treatment outcomes as well as incidence of toxicity (4). They are associated with various toxicities such as nephrotoxicity, ototoxicity, and neurotoxicity (7). Several factors contribute to their toxicity profile and these include dehydration, kidney function derangements, increased frequency of dosing, raised trough concentrations, and prolonged duration of therapy (8).

Several guidelines require that patients who are to be treated using an aminoglycoside should have a kidney function test done before the commencement of treatment and subsequent monitoring should be done at least twice weekly (9–11). Therapeutic drug monitoring is also recommended in patients receiving any aminoglycoside (12) to monitor toxicity and treatment efficacy which allows for dose adjustment if necessary (5,11,13,14).

1.2 Study problem

Aminoglycosides are widely used in Kenyatta National Hospital (KNH). A recent study done in 2019 found that the major indication for these drugs was neonatal sepsis (15) and the overall use in pediatrics was 9.8% with the newborn unit having a higher prevalence of use at 16.2%. Gentamicin and amikacin are the most commonly used drugs in this class of antibiotics, the prevalence of use was 5.1 and 4.7% respectively. The most common guidelines used in KNH are the Basic Pediatric Protocol issued by the Ministry of Health (6) and the WHO Pocket Book for Hospital Care (16) which guide in the choice of antibiotics and dosage calculations.

Despite being very effective in the management of severe infections in pediatrics, aminoglycosides have a narrow therapeutic index and can cause ototoxicity (17). The incidence of early hearing impairment in neonates and children is reported to be low which may be due to limited data available on aminoglycosides induced hearing loss. Several studies report an incidence of 7-90% (19).

In KNH, kidney function tests are not routinely done before and after the commencement of treatment with aminoglycosides. This, therefore, means that the true incidence of aminoglycoside-induced toxicity among neonates remains unknown. In addition, therapeutic drug monitoring is not routinely done in neonatal patients who are put on this medication. As a result of lack of measurement of drug serum levels, these patients may be overdosed therefore predisposing them to toxicity.

To date, there are no studies that correlate aminoglycoside trough levels in pediatric patients and kidney function as well as other risk factors for toxicity. There is also lack of clinical experience in the public sector in Kenya with regard to therapeutic drug monitoring of aminoglycosides. This

means that pediatric patients are highly susceptible to sub-therapeutic or toxic drug exposure. There are no protocols to guide dose individualization at KNH. This study determined the incidence of hearing loss and the influence of aminoglycoside serum trough levels on kidney function and whether therapeutic concentrations were achieved in the pediatric patients.

1.3 Research questions

1. What are serum trough levels of aminoglycosides in pediatric patients admitted in Kenyatta National Hospital?
2. How is the renal function of pediatric patients treated with aminoglycosides in Kenyatta National Hospital?
3. What is the incidence of early hearing impairment in pediatric patients treated with aminoglycosides in Kenyatta National Hospital?

1.4 Objectives

1.4.1 Main objectives

To determine aminoglycoside serum trough levels, renal function and the risk of early hearing loss among pediatric patients admitted at Kenyatta National Hospital.

1.4.2 Specific objectives

1. To determine if the serum trough levels of aminoglycosides in pediatric patients admitted in Kenyatta National Hospital are within therapeutic range.
2. To measure the decline in kidney after treatment initiation with aminoglycoside and to establish the prevalence of aminoglycoside induced kidney injury.
3. To determine the prevalence of early hearing loss in patients treated with aminoglycosides.

1.5 Significance

Studies have shown that the use of aminoglycosides in pediatric patients can cause early hearing loss with some reporting an incidence of ototoxicity as low as 7% and some as high as 90% (18). Most studies reported the incidence of ototoxicity in patient populations in whom monitoring and dose individualization was not done adequately (5,18,19). Aminoglycosides are extensively used in KNH especially in the newborn unit for the management of sepsis and pneumonia where therapeutic drug monitoring and kidney function tests are not routinely done. This study has described aminoglycoside serum trough levels and the risk early hearing impairment and renal function among pediatric patients admitted at KNH.

The results of the study will influence the development of protocols and guidelines for aminoglycoside use which will help in dose calculation and monitoring. It will also encourage teamwork between physicians and clinical pharmacists in patient care to enable individualization of treatment among pediatric patients since therapeutic drug monitoring requires specialized competency in pharmacokinetics. This will help minimize drug-related toxicity and improve patient outcomes as well as reduce the duration of hospitalization and costs to the patients.

In Kenya, Therapeutic Drug Monitoring (TDM) remains poorly developed largely due to limited resources. This study has demonstrated the importance of monitoring drug concentrations and kidney function in patients receiving aminoglycosides.

CHAPTER TWO: LITERATURE REVIEW

2.1 Aminoglycoside use in pediatric patients

It is estimated that 3 million infant deaths occur annually of which an estimated 36% are associated with neonatal septicemia (20). Bacterial infections are the major cause of death in children (2) and antibiotics are commonly used in pediatrics as empiric or targeted therapy (21). Several guidelines recommend the use of penicillin with gentamicin as a first line treatment unless culture and sensitivity studies in the region indicate high patterns of resistance (22,23).

In Kenya, the pediatric protocol recommends initiation of gentamicin and penicillin if a patient shows signs of sepsis and it also recommends antibiotic prophylaxis with these drugs be initiated soon after birth (6).

Aminoglycosides are used in the management of severe infections due to gram-negative bacterial infections (4) such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus*, *Klebsiella*, *Enterobacter* and *Acinetobacter* (24). They are dosed in different ways; the traditional dosing, that is the small dose-short interval dosing or the large dose-extended interval dosing also known as the once daily dosing. The dose is calculated based on the patient's gestational age and weight. Administration of a large once daily dose is supported by the fact that aminoglycosides have a concentration-dependent bactericidal activity and a post-treatment effect, thus this maximizes bacterial kill rate and the post-treatment effect is preventative of bacterial re-growth (5).

2.2 Pharmacokinetics of Aminoglycosides

Aminoglycosides have a narrow therapeutic window and therefore the dosing and pharmacokinetics of this class of drugs are important determinants of treatment outcomes as well as incidence of toxicity (6). Generally, they have a low protein binding capacity of less than 10%,

are widely distributed in extracellular fluid and have a low volume of distribution (VD). In neonates, the dosing of aminoglycosides is complicated by the fact that they have a unique physiology (7,25). In neonates a high VD and a decreased protein binding (8) leads to high concentrations of the free drug in plasma and large VD in extracellular fluid (9).

Pathophysiological changes that occur in critically ill patients may cause changes in VD and clearance of aminoglycosides, complicating the dosing of these drugs even further. For example, patients with sepsis, fever, congestive heart failure and severe burns tend to have a higher VD due to movement of fluid from intravascular to interstitial space (9). This increase in VD may result in sub therapeutic levels of aminoglycosides if dosing is not adjusted. Therefore, when dosing, the initial and maintenance dose should be based on volume of distribution and clearance respectively (11).

2.3 Aminoglycoside toxicity and associated risk factors

Another consequence of their narrow therapeutic index is that aminoglycosides have been associated with various toxicities such as nephrotoxicity, ototoxicity and neurotoxicity (10). Several factors contribute to their toxicity profile such as dehydration, associated pathology of the kidneys, and increased frequency of dosing, trough concentrations, and prolonged duration of therapy (10).

Aminoglycosides are a well-known cause of drug-induced kidney problems. The incidence of nephrotoxicity of this class of antibiotics has risen from 2-3% to 20% in the past ten years (12). These drugs are polycationic in nature thus have a poor oral bioavailability and a high renal clearance. This cationic charge is suspected to be the cause of nephrotoxicity (12). The use of nephrotoxic drugs may lead to acute kidney injury. Acute Kidney Injury (AKI) is the sudden

decline in renal function over a specified period of time shown by an increase in serum creatine by ≥ 0.3 mg/dL within 48hours or ≥1.5 times the baseline levels which is thought to have occurred within the previous 7 days (13).

Therapeutic drug monitoring is also recommended in patients receiving an aminoglycoside. As already mentioned, the pharmacokinetic profile of aminoglycosides may be altered in patients with severe sepsis, burns, ascites and renal replacement therapy. Therefore, it is important to monitor plasma concentrations from the initial dose to optimize the dosing regimen (13)

Amikacin is a bactericidal aminoglycoside with the broadest spectrum of activity. It is resistant to aminoglycoside inactivating enzymes thus is very useful in hospitals where there is a high prevalence of gentamicin and tobramycin- resistant micro-organisms. Studies have shown that it is effective against neonatal sepsis, bone and joint infections, skin and soft tissue, respiratory tract, central nervous system and intra-abdominal and urinary tract infections as well as in burns. It is commonly used either as a single agent or in combination with other antibacterials (6,8). In Kenya amikacin is an essential drug used in neonates for the management of severe gram negative infections which are gentamicin resistant (8).

Amikacin has a narrow therapeutic window and is associated with serious adverse drug reactions that are typical of aminoglycosides, such as nephrotoxicity (10), ototoxicity (12) and neurotoxicity (11). Neonates are particularly susceptible to toxicity since there have been limited number of studies done in this group of patients (10). Clinical trials are hardly conducted in pediatric patients due to ethical concerns (12) and therefore there is limited data drug pharmacokinetics efficacy and safety of amikacin in this population (10).

Certain factors may put patients at increased risk for toxicity (10). Aminoglycoside otoxicity is more likely to occur with higher doses, higher serum trough levels, or prolonged duration of therapy (12). Other high-risk patients include underweight patients, those with renal problems, those with a hearing problem, those with a family history of ototoxicity, and those receiving diuretics such as loop diuretics or other ototoxic or nephrotoxic medications (12).

2.4 Epidemiology of ototoxicity

Aminoglycosides have the potential to cause ototoxicity, which manifests as vestibular toxicity and hearing loss. According to Sonia et al these drugs have the potential to cause irreversible hearing loss (28). Vestibular toxicity can lead to loss of balance and oscillopsia, a visual disturbance in which objects in the field of vision appear to swing in a regular rhythm (28). The ototoxic effects vary within the class of aminoglycosides; gentamicin affects both the vestibular and cochlear system, streptomycin and tobramycin are mainly vestibulotoxic, while amikacin, kanamycin, and neomycin are preferentially cochleotoxic (28). This is due to the fact that the rate of aminoglycoside clearance from the inner ear fluid is slower than the clearance from serum. This phenomenon can lead to the onset of hearing loss or progression of hearing loss after stopping aminoglycoside therapy. Studies on amikacin carried out in neonates showed that it can cause severe, moderate and mild sensorineural hearing loss (29,30).

2.5 Monitoring aminoglycoside toxicity

Patients on aminoglycoside treatment require serum concentration to be monitored closely to ensure that the treatment is efficacious and safe (31,32). Monitoring for toxicity of aminoglycosides can be done using several methods such as patient reporting, testing end organ effect through measuring serum creatinine and hearing tests as well as active bedside testing and therapeutic drug monitoring (TDM) (33, 36).

Therapeutic Drug Monitoring is the measurement of serum concentration of a medication at a single or multiple time points with the aim of using these concentrations to manage patient's medication requirements and individualize doses in order to optimize clinical outcome and minimal adverse effects especially for drugs with a narrow therapeutic index (34,35). The most common antibiotics subjected to TDM are aminoglycosides such as gentamicin, amikacin, and tobramycin (33,35, 40,41).

Algorithms and nomograms have been prepared for aminoglycoside dose individualization and monitoring and they can be derived from a linear regression analysis, population methods, and Bayesian estimation procedures (33). Gentamicin is said to be safe if the trough serum concentrations are 0.5-2 mcg/mL and amikacin is <1 mcg/mL (44). Drugs that are administered at regular intervals accumulate in the body until a steady state is reached where the rate of drug elimination equals the rate drug absorption (40).

Several guidelines suggest that patients who are to be treated using any aminoglycoside should have a kidney function test done before commencement of treatment to measure urea, electrolyte and creatinine (EUC). Subsequently, EUC monitoring should be done in all stable patients and frequency increased in patients with renal impairment. For patients on aminoglycosides for periods longer than 1 month, EUC monitoring should be done twice weekly, weekly and fortnightly in the 1st, 2nd and 3rd month respectively (11,12).

Aminoglycoside ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus and this hearing loss is usually irreversible (28). The usual time of onset is often unpredictable, and marked hearing loss can occur even after a single dose (28,29).

Additionally, hearing loss may not manifest until several weeks or months after completion of antibiotic or antineoplastic therapy (30).

Vestibular injury is also a notable adverse effect of aminoglycoside antibiotics and may appear early on with positional nystagmus (28,30). If severe, vestibular toxicity can lead to dysequilibrium and oscillopsia (28,29).

2.5 Conceptual framework

The conceptual framework is presented in figure 2.1 and it summarizes the different variables that affect aminoglycoside serum levels and hearing acuity in pediatric patients. These two variables are the key dependent (outcome) variables under investigation. The conceptual framework shows the causal pathway for aminoglycoside serum levels and the main determinant, in this case, is the dose of aminoglycosides.

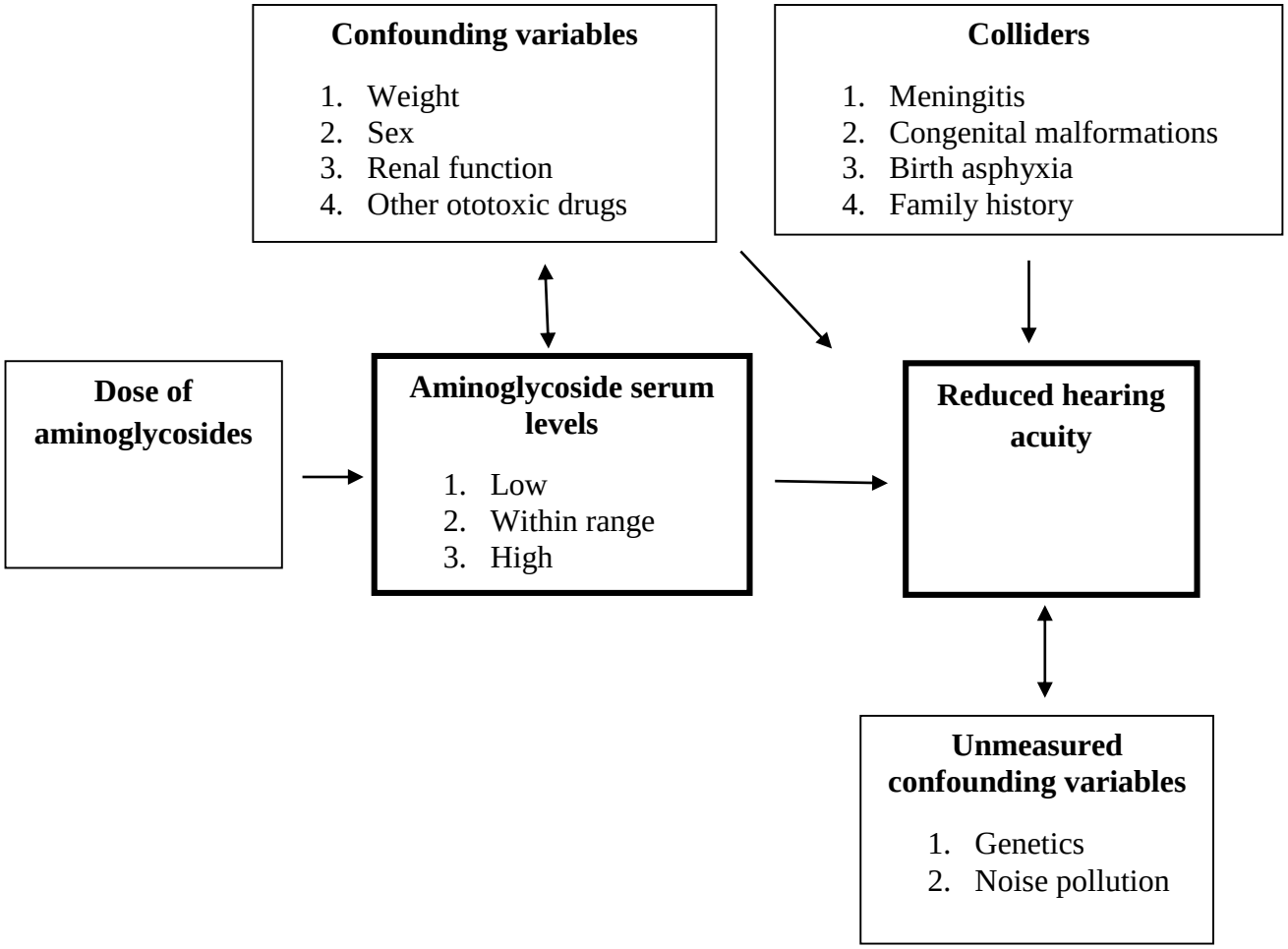

Figure 2.1: Conceptual framework for determinants of aminoglycoside serum levels and reduced hearing acuity

Child-related factors that affect the levels that were investigated included sex, weight, renal function and other ototoxic medication. Collider variables included meningitis, congenital malformations, birth asphyxia and family history of deafness. These are third variables that are risk factors for the outcome but are not associated with the main predictor variables, which in this case are aminoglycoside serum levels. Unmeasured third variables that were not be considered in this study are exposure to noise pollution and genetic determinants of hearing loss.

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a prospective descriptive cohort study that was conducted on pediatric participants receiving aminoglycoside therapy at KNH. Trough levels of aminoglycosides, incidence and risk factors for early hearing loss and renal function in pediatric participants were measured prospectively. The study was carried out from May to September, 2018.

3.2 Study site

The study was conducted in the pediatric wards 3 (A, B, C, D) and the newborn unit (NBU) of Kenyatta National Hospital (KNH). This hospital was selected because it is the largest referral hospital in Kenya. It hosts a diverse group of patients from different regions, ethnic backgrounds and socioeconomic status. It has a pediatric unit in which many of the patients are treated with aminoglycosides and this made it a suitable study site. It also has specialists in pediatrics, nephrology, clinical pharmacy, clinical pharmacology and pharmacoepidemiology and pharmacovigilance. The hospital is a training site for the College of Health Sciences, University of Nairobi and works in collaboration with many other institutions in offering clinical services (41).

3.3 Study population

The study population consisted of children aged 5 years and below admitted in KNH during the study period who were receiving treatment with an aminoglycoside.

3.3.1 Inclusion and exclusion criteria

A cohort of pediatric patients aged 5years and below admitted in Kenyatta National Hospital during the study period, who received aminoglycoside treatment, whose parents/guardians/care

givers provided voluntary informed consent to be part of the study were prospectively recruited. Those on any other drugs other than aminoglycosides and with a pre-existing hearing impairment were excluded.

3.5 Sample size considerations

Given that the study design was a descriptive cohort study, the Cochran formula for calculating sample size (Equation 1) was used to estimate the sample size. This formula was appropriate for this study since the aim was to determine the incidence of ototoxicity amongst patients on aminoglycoside therapy. According to the WHO, the incidence of ototoxicity in aminoglycoside treated patients was 25% (42).The level of significance, alpha was set at 0.05 and the margin of error at 0.05.

Equation 3.1: Conchran formula for computation of sample size

$$\boldsymbol{n = \frac{Z\text{^}2 \times p(1-p)}{d\text{^}2}}$$

Where

n= the calculated sample size

Z = the t statistic for a level of significance of 5%, Z = 1.96

p = the expected incidence of aminoglycoside induced ototoxicity (the WHO estimate of the incidence of aminoglycoside induced ototoxicity is 25%, then p = 0.25) and

1-p = is 0.75

d = Precision (in this case the precision is 5%, therefore d = 0.05)

Using these parameters, the estimated sample size was 288. Given that the study was conducted on a finite population estimated at 300 the correction for a finite population was applied using equation 2

Equation 3.2: Cochran formula for a finite population correction

$$n' = \frac{no}{1 + \frac{(no-1)}{N}}$$

Where

n' = Sample size after a finite population correction,

n_o = sample size derived from equation (3.1)

N = population size,

However, the estimated patient population during the study period was 300 and n/N is > 0.05 thus the finite population correction was applied (equation 3.2).

Using these parameters, the minimal targeted sample size was 147.

3.6 Participant recruitment and sampling methods

From the outpatient pediatric unit, we identified pediatric patients who met the inclusion criteria who were to be admitted using the eligibility checklist in appendix A, before administration of written informed consent in appendix B. The list of patients who met the inclusion criteria on each day formed the sampling frame. After the list was obtained, a bedside visit was made and the parent/guardian/care giver was approached and given information about the study with the aid of the informed consent form (appendix B). The parent/guardian/care giver were informed that there

was no coercion to join the study and their refusal would not affect the subsequent quality of care they were to receive.

Universal sampling was employed, whereby all patients whose parent/guardian/care giver gave informed consent were recruited into the study until the desired sample size was attained. The patients were recruited only if the parent/guardian/care giver gave informed consent. Subsequently, the recruited participants were followed up twice daily until the day of discharge.

Recruitment was not done during clerking, ward rounds or when nurses were administering treatment to minimize interruption of the normal workflow. I did not alter the participant's treatment but if toxicity was noted the clinicians were advised on treatment adjustment based on the determined trough levels.

3.7 Data collection

3.7.1 Data collection instrument

Data collection tool was a data abstraction form in appendix C that was designed and tested and validated prior to data collection. This was done to ensure that all the required information was collected so as to address the study objectives.

3.7.2 Abstraction of data from patient records

The data sources that were considered in this study included patient files, treatment sheets and laboratory reports. sociodemographic information such as the ward, gender, county of residence, age, birth weight, current weight and height were obtained from patient files. Additional information that was abstracted from the patient files included risk factors such as the indication for treatment, history of malformation, hearing loss, human immunodeficiency status, history of

use of ototoxic and nephrotoxic medication, comorbidities as well as a history of birth asphyxia. The treatment sheets gave a list of the medications the participant was on while admitted and the medications that had a potential for drug-drug interactions. Lab records were also looked at and data on the Urea and electrolytes, trough levels and the results for the hearing screening tests were obtained. Participants records were reviewed at least twice daily during hospitalization so as to collect and update information. The data collection form is appended (Appendix C)

3.7.3 Determination of renal function

Urea, electrolytes, and creatinine (UEC) were measured twice for each patient (before initiation of therapy and after treatment initiation). Approximately 2.0 ml of blood sample was collected by a qualified phlebotomist before initiation of aminoglycoside therapy to determine baseline UECs and another 2.0 ml of blood was collected from the patients after 72 hours for the determination of follow up UECs to measure kidney function. Laboratory analysis was done in the KNH Renal Laboratory. Estimated glomerular filtration rate (eGFR) was also calculated using the Schwartz equation 3.

Equation 3

$$\mathbf{eGFR(mL/min)/1.73m2) = k * Height(cm) \div serum\ creatinine\ (mg/dL)}$$

3.7.4 Determination of aminoglycoside serum trough levels

3.7.4.1 Blood sample collection and drug assay

Serum aminoglycoside trough levels were measured before administration of the third dose of the aminoglycoside to determine if the trough levels were within therapeutic range. 2.0 ml of the blood sample was collected by a qualified phlebotomist under careful supervision of the principal investigator before administration of the third dose for the determination of serum trough levels. The blood specimen was collected using the red-top tube for collection of serum, coated with silicon for accelerated clotting, through a venipuncture 30 minutes before the next dose. The blood sample was stored in an icebox at 4^{o}C (because failure to freeze samples containing antibiotics could cause in vitro inactivation producing falsely low aminoglycoside levels) and was immediately transported to the biochemistry laboratory of Nairobi Hospital. The sample was analyzed within 30minutes of the collection to minimize degradation.

The specimen was analyzed in Nairobi Hospital by a qualified laboratory technologist with adequate knowledge to carry out the assay. Since specimens containing particulate matter could produce inconsistent results, the samples were centrifuged at 8,000 to 10,000 relative centrifugal forces for ten minutes to separate particulate matter.

3.7.4.1.2 Assay of Aminoglycoside levels

The ARCHITECT i Gentamicin/amikacin assay is an in vitro chemiluminescent micro-particle immunoassay (CMIA) used for the quantitative determination of gentamicin/amikacin serum or plasma levels, using the STAT protocol capability. The results obtained are used in monitoring treatment efficacy or toxicity of gentamicin/amikacin to help in individualization of therapy.

Multi-agent aminoglycoside kits from Abbott diagnostics automated for use on ARCHITECT Ci8200 were used. This model provides immunoassay and clinical chemistry testing in a single integrated system and it can handle a huge workload that is a maximum of 200 immunoassay and 1200 clinical chemistry tests per hour.

The ARCHITECT i Gentamicin/amikacin calibration was done before the tests were run. The calibrators were set in the range of 0.0-10.0 µg/mL. This was evaluated using commercially available controls, a single sample of all levels of controls were tested. To obtain the recommended volume requirements for the ARCHITECT i Gentamicin/amikacin Calibrators, the bottles were held vertically, and 5 drops of each calibrator were dispensed into each respective sample cup. The manufacturer's instructions were followed for preparation of commercially available control material. It was important to ensure that assay control values were within the established ranges. Once the ARCHITECT i Gentamicin/amikacin calibration was accepted and stored, all subsequent samples were tested without further calibration.

This was a one-step immunoassay for the quantitative determination of aminoglycoside trough levels in serum. In the ARCHITECT i assay, sample, anti-gentamicin or anti-amikacin coated paramagnetic micro-particles, and gentamicin/amikacin acridinium-labeled conjugate were combined to create a reaction mixture. The anti-gentamicin/amikacin coated micro-particles bound to the gentamicin/amikacin present in the sample and to the acridinium-labeled conjugate. After washing, pre-trigger and trigger solutions were added to the reaction mixture. The resulting chemi-luminescent reaction was measured as relative light units. An indirect relationship usually exists between the amount of gentamicin in the sample and the relative light units were detected by the ARCHITECT i System optics.

This assay technique was a particle-enhanced turbidimetric inhibition immunoassay technique. It was based on a competition between the drug-coated onto a micro-particle for antibody binding sites of the aminoglycoside antibody reagent and the drug in the sample. In the presence of the anti-aminoglycoside antibody reagent and the absence of any competing drug in the sample, the aminoglycoside-coated micro-particle antibody reagent was rapidly agglutinated. When a sample containing aminoglycoside was added the agglutination reaction was partially inhibited, lowering the rate of absorbance. The rate of absorbance was directly proportional to the rate of agglutination and the change in the rate of absorbance was photo-metrically measured. A concentration-dependent agglutination inhibition curve was obtained with a maximum rate of agglutination at the lowest aminoglycoside concentration. The results were reported as micrograms per milliliter (µg/m).

3.7.5 Determination of Hearing acuity

3.7.5.1 Instrumentation and specification

One AUDX.Pro Distortion Product Oto-acoustic Emission (DPOAE) screening instruments shown in figure 3.1 was used to conduct the hearing test. The model was Echo- Screen TS ref: 580-AXPBOX-041 manufactured by Natus Medical Inc., San Carlos, California, USA. The instrument was validated and calibrated before commencement of the study.

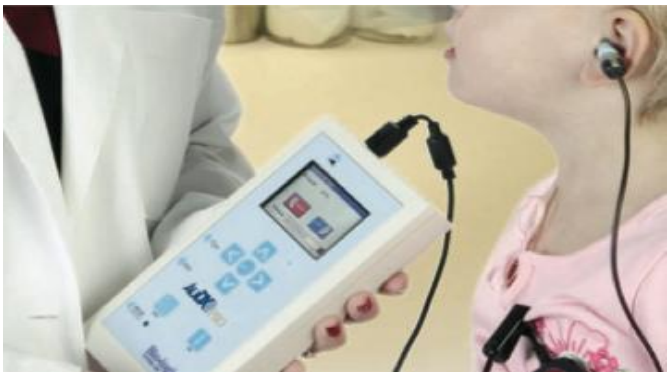

Figure 3.1: AUDX. pro DPOAE instrument that was used to screen for hearing loss in pediatric participants who were treated with an aminoglycoside at Kenyatta National Hospital.

The AUDX.pro system includes: 100 test memory, Distortion Product Oto-acoustic Emission and Transitory Evoked Oto-acoustic Emission screening protocols and an Additional (3) DP protocols Protocol Setup Software. It can test 12-frequencies within a single protocol.

3.7.5.2 Participant Preparation, Hearing Test Procedure and Interpretation

This instrument was used as a screening test for hearing loss before and after treatment with aminoglycosides. The participants ear canal was examined with an otoscope prior to insertion of the ear tip into the ear so as to ensure the ear canal was free from earwax which could interfere with the DPOAE test. A disposable ear tip that was appropriate for the size of the participant's ear canal was selected and installed on the probe. An ear tip that is too small could result in low stimulus intensity and could cause a refer result. The ear tip was then inserted into the patient's ear canal. It was then held in place for a few seconds while the foam expanded in the canal. The probe was not held in place as this would create noise.

It presented two soft tones (distortion product oto-acoustic emissions) to the participant's ears through a probe with a small microphone placed in the ear canal. The microphone measured the

oto-acoustic emission (OAE) then it automatically made a comparison with the normal. The advantages of this test included the fact that: it is an objective test since the participant's response was not required, it presents the results as either a pass or refer therefore no further interpretation was needed and it gave fast and accurate results. The output/results of the test were presented as a pass or refer on the screen. The system default DPOAE protocol stops the test when the conditions for an overall test Pass or Refer occur.

The first hearing screening was conducted prior to treatment with aminoglycosides and the second one, prior to discharge of the child after treatment had been completed. The DPOAE hearing screen was considered an "overall pass" result when at least three pass results were obtained out of the five frequencies tested between 2-6 kHz in each ear. The DPOAEs equipment displayed the results of each ear tested as either a "pass" or "refer". If the child failed, they were referred to the ENT Clinic in KNH.

3.7 Variables and definitions

3.7.1 Variables

Two outcome variables were investigated in this study. These variables included the continuous variable aminoglycoside serum trough levels and the categorical variable presence or absence of hearing loss. For the aminoglycoside levels, the predictor variables that were dose, sex, body weight, height, body mass index time since the last dose and renal function measured using estimated GFR. For hearing acuity, the potential predictor variables that were evaluated was aminoglycoside trough levels, sex, meningitis, history of being put on oxygen and family history of hearing loss. unmeasured confounders such as noise pollution and genetic determinants of hearing loss were not recorded.

3.7.2 Definitions

According to literature optimal trough level values for gentamicin is 0.5-2 mcg/mL and amikacin is <1 mcg/mL. Participants were categorized as being in the sub-therapeutic for gentamicin levels <0.5 and amikacin levels < 1 mcg/mL, therapeutic for gentamicin levels between 0.5-2 mcg/mL and supra-therapeutic levels for gentamicin levels >2 mcg/mL and amikacin levels > 1 mcg/mL based on the reference values (44).

Acute kidney injury (AKI) was classified using the pediatric modified RIFLE (pRIFLE) based on severity. Estimated creatinine clearance (Cr) was categorized as Risk (R), Injury (I) or Failure (F) if estimated creatinine clearance is reduced by 25, 50 or more than 75 respectively from the baseline.

The hearing screening equipment displayed the results of each ear tested as either a "pass" or "refer". Pass means the participants does not have a hearing problem and refer means the participant has hearing loss and should be sent for further tests to determine which specific hearing problem they may have developed.

3.8 Data Management and Quality assurance

The study was done by the researcher, with the aid of two research assistants, who ensured the smooth running of project activities as per the protocol. The researcher conducted a two-day focused training for the research assistants on the procedures for screening for hearing loss using the DPOAEs equipment. Data collection tools were tested and validated prior to data collection. This was done to ensure that all the required information was collected so as to address the study objectives. Data collection forms were checked daily for completeness and consistency before data entry into Kobo Toolbox was done.

3.10 Data analysis

This statistical analysis was done using STATA version 13.0. All data were subjected to descriptive data analysis and was reported using tables and graphs. Continuous variables such as aminoglycoside serum trough levels were tested for normal distribution using the Shapiro Wilk test and histograms. Summary data analysis was done where all the baseline characteristics of the participants as well as co-morbidities and medications taken by the patient were summarized. Mean and standard deviation of the mean or median and inter quartile range were used depending on whether the variables are normally distributed or not. Categorical variables such as presence or absence of hearing loss were presented as proportions.

Exploratory data analysis was done to compare the baseline demographic characteristics and clinical characteristics of participants with and without reduced hearing acuity the paired t-test was used to compared kidney function before and after treatment. Linear regression was done to determine risk factors for aminoglycoside levels. Parameters were estimated using ordinary least squares. Model building was done using a forward stepwise approach. The coefficient of determination was used to compare models. Multivariate analysis was done to adjust for confounding. Logistic regression was conducted with model building was done as described for linear regression. The adjusted odds ratios were obtained by multivariable regression analysis. The level of significance was set at 0.05.

3.11 Ethical considerations

Ethical approval to conduct the study was obtained from the KNH/UON research and ethics committee (KNH/UON-ERC), approval number P697/12/2017 attached in appendix E. Institutional approval was also obtained from KNH. Informed consent was obtained from the

parent/guardian/caregiver of all the patients from whom data was to be collected after adequate explanation of the study including its aim and requirements.

There was a direct benefit to the patients in terms of dosage adjustments where it was necessary. The findings from the study were communicated to the healthcare workers in the department and the hospital in general. The names of the patients were not used. All data was coded and stored in a password-protected electronic record to ensure confidentiality. Databases were only accessible to the principal investigator and the statistician.

CHAPTER FOUR: RESULTS

4.1 Participant recruitment

Figure 4.1 is a consort diagram that summarizes the number of pediatric patients hospitalized between May and September, 2018. In this period 1425 pediatric patients were admitted. The prevalence of aminoglycoside use amongst pediatric and neonatal patients was 57%; out of these only 30% were eligible for inclusion into this study. The care givers of 250 patients were approached and the non-participation rate was (110, 44%). The care givers who declined felt that the patients were too ill to participate in the study.

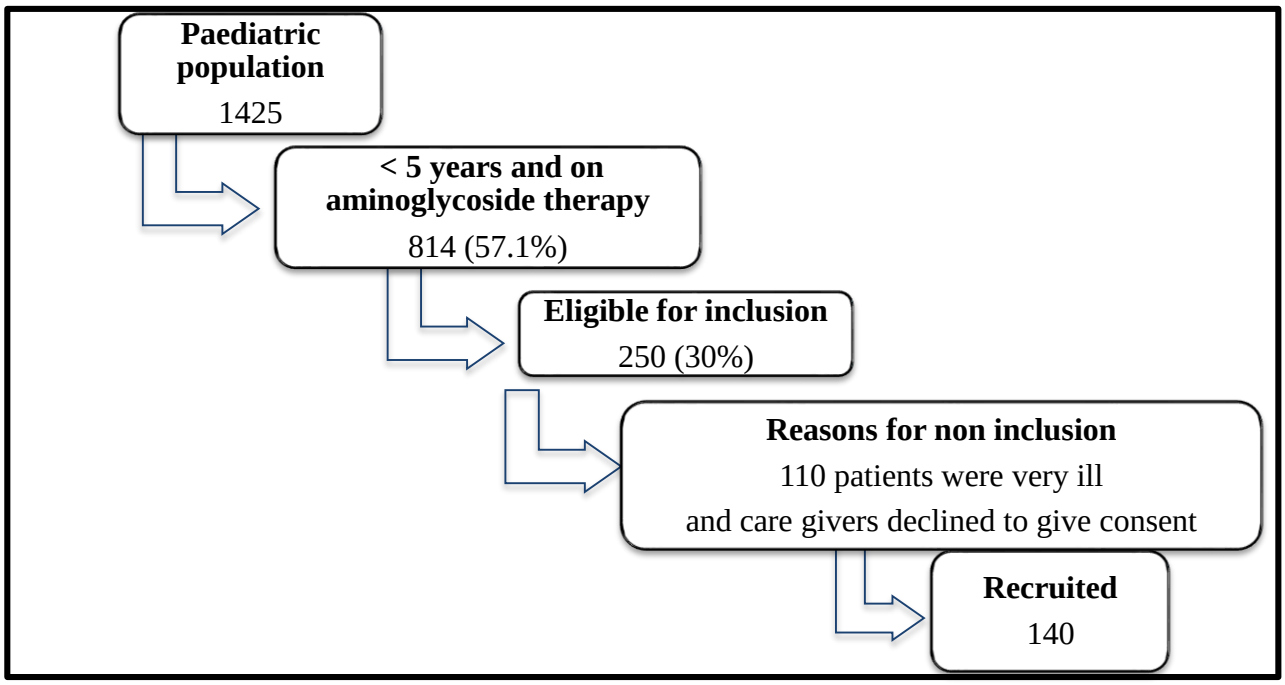

Figure 4.1: Consort diagram showing participant recruitment in the study

Relatively equal numbers were drawn from all the pediatric wards (3A, 3B, 3C and 3D) with the exception from newborn unit where only 14 (10%) care givers gave consent to participate. Ward 3A, B, C, and D had 29 (20.7%), 33(23.6%), 34 (24.3%) and 30 (21.4%) respectively.

4.2 Demographic characteristics of the pediatric participants on aminoglycosides

The participant demographic and clinical characteristics are summarized in tables 4.1 and 4.2.

Table 4.1: Demographic characteristics of the Participants on aminoglycoside therapy in KNH

Characteristics	n	%
Gender		
Male	64	45.7
Female	76	54.3
Total	140	100
Age		
Median 8 [1-18]		
Neonate (0-29 days)	23	16.4
Infant (30 days– 23 months)	91	65.0
Young (24 months- 72 months)	26	16.6
Total	140	100
Birthweight (g)		
Mean 2.9 [0.64]		
<1000g	10	7.1
< 1001 -1500g	4	2.8
<1501- 2500g	25	17.8
>2500g	111	79.3
Total	140	100
Height (cm)		
Median 63 [37-88]		
20-39 cm	1	0.7
40-79 cm	138	98.6
80-120 cm	1	0.7
Total	140	100
Body Mass Index (kilograms/meters^2)		
< 5th percenitile	110	78.6
5th percentile - < 85th percentile	29	20.7
8th – 95th percentile	1	0.7
Total	140	100
Body surface area (meters^2)		
< 0.5m^2	120	85.7
> 0.5m^2	20	14.3
Total	140	100

There were fewer male participants 64 (45.7%) compared to the females 76 (54.3%) participants.

Most of them were infants 91(65.0%), young children 26 (16.6%) and neonates 23 (16.4%) formed

a small fraction of the study population with a median age of 10 [IQR 5-22] months and a median weight of 8[IQR 5-10] Kgs at the time of recruitment. The median body mass index for male and female was 15 [11.6-18.3] and 14.2 [12.1 – 16.7] kilograms respectively. Most of the participants were underweight, 49 (76.6%) male and 61 (80.3) females. Body surface area for most of the participants 120 (14.3%) was less than $0.5m^2$.

Table 4.2: Clinical characteristics of pediatric participants on aminoglycoside therapy at Kenyatta National Hospital

Characteristics	n	%
Indication		
Pneumonia	116	82.9
Sepsis	24	17.1
Total	140	100
Aminoglycoside therapy		
Amikacin	30	21.4
Gentamicin	110	78.6
Duration of hospitalization (days)		
Median 7 [5-10]		
1- 6.9 days	75	53.6
7- 14 days	41	29.3
>14 days	14	10
total	140	100
Treatment outcome		
Temperature	122	87.1
<37°C	18	12.9
>37°C	140	100
Recovery		
Malformations		
Yes	12	8.6
No	128	91.4
Family history of hearing loss		
Yes	3	2.1
No	137	97.9
History of Renal impairment		
Yes	2	1.4
No	138	98.6
HIV positive		
Yes	2	1.4
No	138	98.6
Birth asphyxia		
Yes	16	11.7
No	84	88.3

The most common reasons for admission was pneumonia 116 (82.9%) and sepsis 24 (17.1%) and some of the participants had more than one reason for admission 43(30.7%). For most patients (122, 86.5%) the clinical signs such as fever and laboratory findings resolved within 5-10 days however some (19, 13.5%) were in hospital for a longer period of times. There was a significant reduction in body temperature ($p < 0.001$) after treatment with aminoglycosides Figure 4.2 shows a comparison of the participant's body temperatures before and after aminoglycoside therapy.

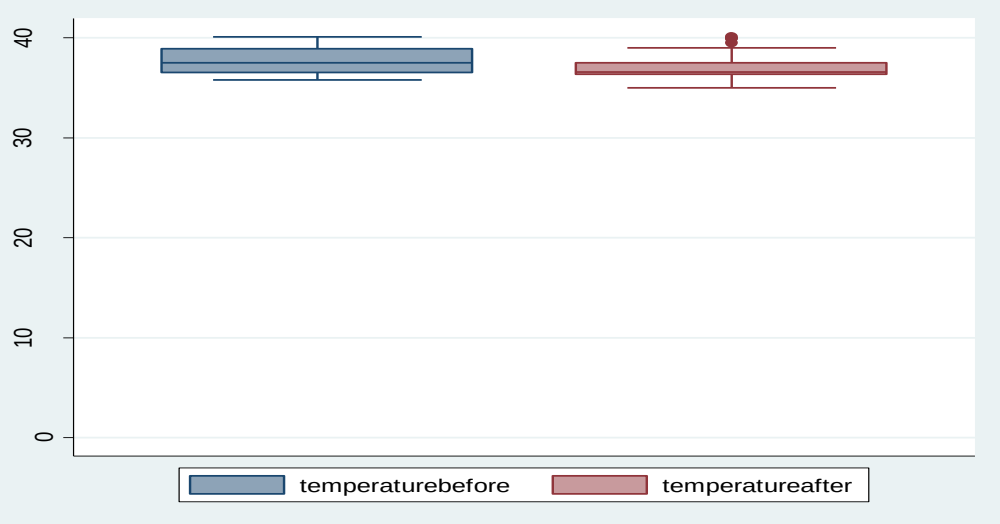

Figure 4.2: A comparison of body temperature before and after aminoglycoside therapy in pediatric participants at KNH

Some of the participants had a history of congenital malformations and birth asphyxia (16, 11.43%) and (12, 8.57%) respectively which are known risk factors for hearing loss. While 2 (1.4%) were HIV positive and a history of renal impairment and 3 (2.1%) had a family history of hearing loss.

4.3 Aminoglycoside therapy

Table 4.3 summarizes the participant characteristics categorized by aminoglycoside used. Participants on amikacin were significantly older ($p = 0.052$) with a slightly lower current weight

compared to those on gentamicin (p = 0.065) because they were previously treated with gentamicin and there was no resolution of clinical signs of illness. Infants formed the highest number participants (91, 65.0%) followed by young children (26, 18.6%) and neonates (23, 16.4%).

Table 4.3: Type of aminoglycoside therapy in pediatric participants at Kenyatta National Hospital

Characteristic	**Median IQR**	**Amikacin n**	**Gentamicin n**	**P- value**
Sex				
Male		16	48	0.345
Female		14	62	
Total		30	110	
Age (months)				
Amikacin	13 [4-33]			
Gentamicin	7 [1-16]			
Neonate (0-30 days)		3	20	**0.052**
Infant (1month-2 years)		16	75	
Young child (2 – 6 years)		11	15	
Current wt. (kg)				
Amikacin	7.15 [5.6-13.9]			**0.065**
Gentamicin	7.25 [3.2-9.4]			
Height (cm)				0.295
Amikacin	72 [61-84]			
Gentamicin	65 [51-77]			
Dose median (mg/kg)	53 [21,70]			0.067
Duration median (days)	7 [5-7]			**0.041**

4.4 Participants medication history

Out of the 140 participants, 65% and 61.4% had taken potentially ototoxic and nephrotoxic medication respectively prior to admission. Some participants were on one ototoxic or nephrotoxic drugs. While 74% were on both ototoxic and nephrotoxic agents simultaneously. Table 4.4 shows the type of medication the participants had used prior to admission and during the study period.

Table 4.4: Types of medications co-administered to pediatric participants at KNH

Type of medication	Medication	n = 140	Percentage (%)
Ototoxic	Macrolides	88	62.8
	Loop diuretics	4	2.8
	Quinine	2	1.4
	Other	8	5.7
	None	38	27.1
	Total	**140**	**100**
Nephrotoxic	Antimicrobials	76	54.2
	NSAIDS	34	24.2
	Antihistamine	3	2.1
	Antidepressants	7	5
	Diuretics	1	0.7
	Others	1	0.7
	None	18	12.9
	Total	**140**	**100**
Drug interaction	With drug interaction	136	97.1
	No drug interaction	4	2.9

During the study period 102 (72.9%) and 122 (87.1%) were on other co-medications that were potentially ototoxic and nephrotoxic respectively. The most common class of ototoxic medications co-administered with aminoglycosides were macrolides (88, 62%) while the most common class

of nephrotoxic drugs were antimicrobials (76, 54.2%) and NSAIDS (34, 24.2%). These medications were grouped as nephrotoxic or ototoxic.

4.5 Participant renal function

The renal function of pediatric participants on aminoglycoside therapy at KNH was summarized in table 4.5, 4.6 and 4.7.

Table 4.5 participants renal function based on participant's demographic and clinical characteristics

Characteristics	**n**	**Mean creatinine**		**Mean eGFR**	
		Before	**After**	**Befrore**	**After**
Gender				47.6±28.6	
Male	64	0.7±0.3	69.9±26.2	47.7±22.3	40.1± 23.4
Female	76	0.7±0.3	72.4±24.1		41.4±35.9
Total	140				
Age (months)					
Neonate (0-29 days)	23	60.5±27.4	64±24.8	37.4±18.4	39.3±24.2
Infant (30 days– 23 months)	91	63.2±26.5	72.3±24.4	43.6±19.1	38.7±19.3
		62.3±26.4	68±23.8	72.1±34	37.1±22.3
Young (24 months- 72 months)	26	-	-	-	-
Total	140				
Current weight (kilograms)					
Median 7.25 [1.8-36]					
< 5th percenitile	113	61.5±27.2	71±25.7	42.9±19	38.7±32.1
5th percentile - < 85th percentile	26	64.1±27.4	73.6±20.9	66.4±35.6	46.9±17.6
	0	62.5±27.4	70.5±21.3	63.5±27.2	35.4±20.1
8th – 95th percentile	1	-	-	-	-
Total	140	-	-	-	-
History of hearing loss					
Yes	3	65.4±27.7	96.3±13.7	37.6±14.1	34.1±12.5
No	137	62.5±26.4	70.7±24.9	47.9±25.4	40.9±31.0
History of renal impairment	2				
Yes	138	60.5±27.4	94±32.5	42.2±1.9	27.6±11.3
No	140	60.5±27.4	70±28.9	47.7±25.4	41.0±30.9
Total					

There was a significant increase in serum creatinine (p = 0.006) after use of the aminoglycosides as (73, 52.1%) participants had levels above the reference range. Serum urea also increased significantly (p < 0.001).

Table 4.6: Effects of aminoglycoside levels on renal function and electrolyte levels

Renal Function	**Before Mean±SD**	**After Mean±SD**	**Mean Difference (95% C.I)**	**Group differences** P - value
Renal function (eGFR)	47.6±25.2	40.8±30.7	6.8 [2.0 - 11.7]	**<0.001**
Creatinine mmol/L	60.5±27.4	71.2±25.0	-10.7 [-10.7--6.1]	**0.006**
Urea mmol/L	4.7±4.3	6.4±7.6	-1.7 [-1.7 - -0.8]	**0.001**
Sodium mEq/L	136.7±6.5	133.4±7.1	3.3 [2.1 - 4.5]	**0.001**
Potassium mEq/L	4.2±0.6	3.8±10.8	-0.5[-0.5 - 1.3]	0.558

The participants showed a decrease in serum sodium and potassium levels with an increase in Serum creatinine and urea levels. The eGFR reduced after initiation of therapy. According to the pRIFLE classification of kidney injury 37 (26.4%) participants showed acute kidney injury after aminoglycoside therapy of these 23 (16.4%) were female.

Table 4.7: Renal function based on participants characteristics on aminoglycoside therapy at Kenyatta National Hospital

Characteristic	No AKI	pRIFLE R	pRIFLE I
	n (%)	n (%)	n (%)
Gender			
Male	50 (48.5)	6 (33.3)	8 (42.1)
Female		12 (66.7)	11(57.9)
Total	53(51.5)	18 (100)	19 (100)
Age			
Neonate (0-30days)	103 (100)	4 (22.2)	4 (21.1)
Infant (1 month – 2 years)		10 (55.6)	10(52.6)
Young (2 - 6 years)	15(14.6)	4 (22.2)	5 (26.3)
Total	71(68.9)	18 (100)	19 (100)
	17(16.5)		
Current weight (kilograms)	103 (100)		
Median 7.25 [1.8-36]			
< 5^{th} percentile	81(78.6)	15 (83.3)	16(84.2)
5^{th} - < 85^{th} percentile	19 (18.4)	3 (16.7)	3 (15.8)
8^{th} – 95^{th} percentile	3(2.9)	0 (0)	0 (0)
Total	0 (0)	0 (0)	0 (0)
	103(100)	18 (100)	19 (100)
Body surface area (meters2)			
< 0.5m2	89 (87.3)	15 (83.3)	14(73.7)
> 0.5m2	13 (12.7)	3 (16.7)	5 (26.3)
Total	102 (100)	18 (100)	19 (100)
Gentamicin trough levels(mg/dl)			
Sub-therapeutic	49 (60.5)	3 (21.4)	8 (53.3)
Therapeutic	17 (21)	2 (14.3)	1 (6.7)
Supra-therapeutic	15 (18.5)	9 (64.3)	6 (40)
Total	81(100)	14 (100)	15 (100)
Amikacin trough levels (mg/dl)			
Sub-therapeutic	15 (75)	2 (50)	4(100)
Therapeutic	3 (15)	1 (25)	0 (0)
Supra-therapeutic	2 (10)	1 (25)	0 (0)
Total	20(100)	4 (100)	4 (100)

Abbreviations: AKI, acute kidney injury; R, risk; I, Injury; F, failure; pRIFLE, pediatric RIFLE.

4.6 Aminoglycoside trough levels in pediatric participants at KNH

Out of the 140 patients on aminoglycosides 110 (78.6%) were on gentamicin with a median dose of 53mg/kg [21,70] for duration of 7 days [5,7] while 30 (21.4%) patients were on amikacin with a median dose of 105mg/kg [85,210] for duration of 7 days [7,10]. Figure 4.3 are histograms of the aminoglycoside trough levels.

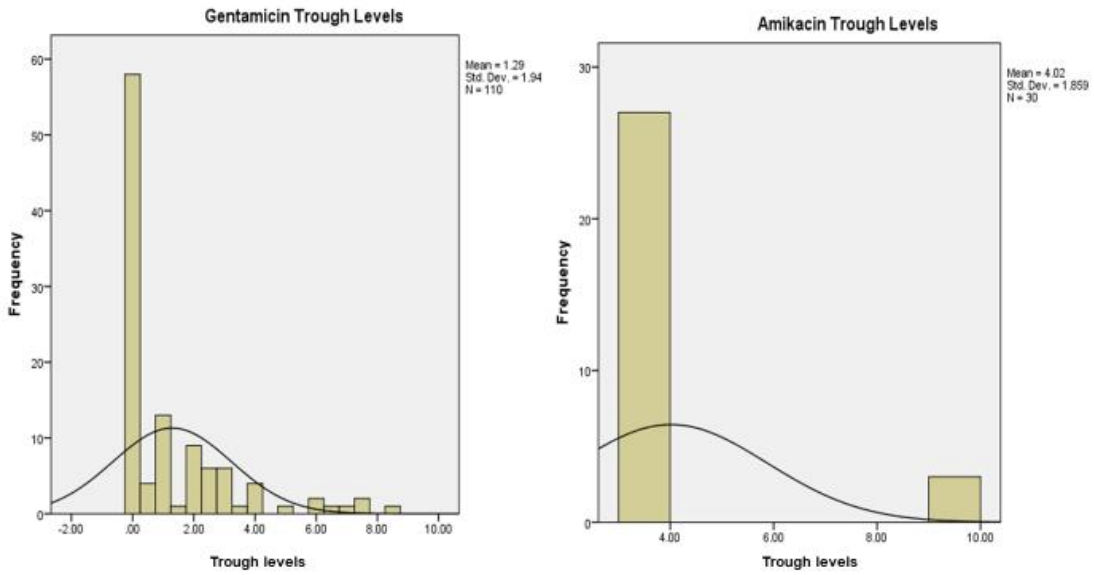

Figure 4.3: a histogram of gentamicin and amikacin trough levels

Most of the participants had aminoglycoside trough levels that were below the therapeutic range. In the gentamicin group, there were 60 (55%) in the sub-therapeutic range, 20 (18%) in the therapeutic range and 30 (27%) in the supra-therapeutic range. In the amikacin group 27 (90%) had sub-therapeutic levels while 3 (10%) of the participants had levels in the supra-therapeutic range.

Most of the participants on gentamicin 60 (54.5%) had sub therapeutic levels. More female participants 32 (53.3%) had sub-therapeutic levels compared to male participants 28 (46.7%).

Also, more female participants had supra- therapeutic levels 17 (56.7%) compared to male participants 13 (46.3%). The participants were classified according to the WHO classification of pediatrics and the trough levels were stratified according to age. This showed that more infants received sub- therapeutic levels 35 (58.3%), the neonates 18 (30.0%) then young children at 7 (11.7%). Also, more infants 24 (80.0%) had supra therapeutic levels compared to the other age categories. Weight was also categorized based on the WHO classification and this stratification showed more participants who were above

4.7 Factors affecting aminoglycoside trough levels

Further analysis was carried out and the results presented in table 4.8 and 4.10. The major determinants of the trough levels were age and weight below 10 kgs. Participants who were in the sub-therapeutic range had a mean age of 10 months. An additional analysis was done to determine how comorbidities and medications affected trough levels but none of the evaluated variables was a determinant of trough levels. There was a significant association between a history of hearing loss and gentamicin trough levels ($p = 0.010$). Inferential analysis was repeated where gentamicin levels were dichotomized as within or outside the therapeutic range.

Table 4.8: Gentamicin trough levels by participant characteristics

Variable	Gentamicin Trough Level			
	Sub-therapeutic n (%)	**Therapeutic n (%)**	**Supra-therapeutic n (%)**	**p- value**
Sex				0.660
Male	28(46.7)	7(35.0)	13(43.3)	
Female	32(53.3)	13(65.0)	17(56.7)	
Total	60	20	30	
Age in Months				**0.014**
Neonate (0-30 days)	18 (30.0)	1 (5.0)	1 (3.3)	
Infant (1month-2 years)	35 (58.3)	16 (80.0)	24 (80.0)	
Young child (2 – 6 years)	7 (11.7)	3 (15.0)	5 (16.7)	
Total	60	20	30	
Current weight (kilograms)				0.075
< 5th percenitile	83 (100)	8 (72.7)	14 (7)	
5th percentile - < 85th percentile		3 (27.3)	2 (18)	
8th – 95th percentile		0 (0)	0 (0)	
		0 (0)	0 (0)	
		11	16	
Malformation	7(11.7)	0(0.0)	1(3.3)	1.137
History of Hearing loss	0(0.0)	2(10.0)	0(0.0)	**0.010**
Renal Impairment	0(0.0)	0(0.0)	1(3.3)	0.260
HIV	1(1.7)	1(5.0)	0(0.0)	0.428
Birth asphyxia	9(15.0)	1(5.3)	3(10.3)	0.497
Put on oxygen therapy	27(45.0)	9(45.0)	13(43.3)	0.988
Ototoxic Medication 1 drug	35(58.3)	11(57.9)	17(56.7)	0.826
2 drugs	3(5.0)	1(5.3)	0(0.0)	
Nephrotoxic1 drug	17(56.7)	10(50.0)	37(61.7)	0.645
2drugs	13(43.3)	10(50.0)	23(38.3)	

Participants who had a history of malformation 7 (11.7%), birth asphyxia 9 (15.0%) and those were put on oxygen 27 (45.0%) had sub-therapeutic levels. Participants who had a previous history of having used ototoxic medication had sub-therapeutic levels while those who had a history of or on other nephrotoxic drugs had supra therapeutic levels.

Linear regression was done to determine the factors associated with gentamicin trough levels summarized in table 4.9.

Table 4.9: Linear regression analysis of factors affecting gentamicin trough levels

Variable	Category	B	S.E	95% C.I.		p-value
				Lower	Upper	
Sex	Male	0.116	0.473	-0.811	1.043	0.806
Age	Months	-0.034	0.031	-0.096	0.028	0.283
Current weight	Kgs	0.099	0.146	-0.188	0.386	0.498
Renal Function	eGFR before	0.005	0.008	-0.011	0.021	0.554
Nephrotoxic Drugs	Yes	-0.744	0.690	-2.097	0.609	0.281
Ototoxic Drugs	Yes	-1.220	1.218	-3.607	1.167	0.317

None of the variables showed a significant association. A further analysis was done for factors associated with sub-therapeutic, toxic levels and outside the therapeutic range. Age p = 0.006, current weight p = 0.028and body surface area p = 0.039 showed a significant association.

Table 4.10: Logistic regression analysis of factors affecting gentamicin trough levels

Parameter	C.O.R	95% C.I C.O.R		P-value
		Lower	Upper	
Age in Months	0.96	0.93	0.99	**0.006**
Birth weight	1.27	0.59	2.74	0.544
Current Weight	0.87	0.77	0.99	**0.028**
Height	0.97	0.88	1.06	0.448
Body Surface Area	0.03	0.00	0.83	**0.039**
eGFRbefore	1.00	0.98	1.02	0.957

Logistic regression was done and the key risk factors identified for sub-therapeutic levels identified were age <18 months (adjusted OR 0.36, 95% CI: 0.14 - 0.92), and weight <10kgs (adjusted OR 0.2, 95% CI: 0.07 - 0.53).

Table 4.11: Factors associated with amikacin Trough Levels in pediatric participants on aminoglycoside therapy

Characteristic	**Detectable levels**	**Non-detectable levels**	**P-Value**
	(n=3)	**(n=27)**	
Age in months	18.7 ± 9.8	20.0 ± 18.9	0.906
Birth weight	2.2 ± 0.3	3.0 ± 0.7	0.960
Current weight	9.7 ± 4.6	9.5 ± 7.2	**0.042**
Height	71.0±23	64.3 ± 9.9	0.726
Body surface area	0.4 ± 0.0	0.4 ± 0.2	0.640
Renal function after	20.2±8.9	39.2 ± 22.0	0.153
Gender – male female	1(33.3%) 2(66.7%)	15(55.6%) 12(44.4%)	0.586
malformation	0(0.0%)	4(14.8%)	1.000
History of hearing loss	0(0.0%)	1 (3.7%)	1.000
With renal impairment	0(0.0%)	1(3.7%)	1.000
Birth asphyxia	0(0.0%)	3 (11.5%)	1.000
on oxygen	2(66.7%)	9(33.3%)	0.537
Ototoxic drug	3 (100.0%)	21(77.8%)	0.592
Total Ototoxic drugs -1 2	3(100.0%) 0(0.0%)	20 (74.1%) 7(25.9%)	0.659
Nephrotoxic drug	3 (100%)	20 (74.1%)	0.564
Total Nephrotoxic drug-1 2 3	3(100.0%) 0 (0.0%) 0 (0.0%)	13(48.1%) 6 (22.2%) 1 (3.7)	0.450

In the amikacin group 27 (90%) had levels below detectable levels while 3 (10%) had supra-therapeutic levels. More males had sub-therapeutic levels 15 (55.6%) compared to females 12

(44.4%). More females 2 (66.7%) had supra-therapeutic levels. Participants with a birth weight of 2.5kgs or greater 19 (70.3%) had lower levels of amikacin in serum.

Current weight was significantly associated amikacin trough levels below the therapeutic range. Participants with levels that were above the therapeutic range had a lower current weight. There was no correlation between the medications co-administered with aminoglycosides which are summarized in appendix D.

Table 4.12: logistic regression analysis of factors affecting amikacin trough levels

Variable	Category	B	S.E	95% C.I. Lower	Upper Lower	p-value
Sex	Male	-0.787	0.878	-2.508	0.933	0.370
Age	Months	-0.020	0.030	-0.080	0.039	0.503
Current weight	Kilograms	0.014	0.098	-0.179	0.206	0.889
Renal Function	eGFR before	-0.001	0.023	-0.046	0.045	0.977
Nephrotoxic Drugs	Yes	0.522	1.402	-2.226	3.269	0.710
Ototoxic Drugs	Yes	0.616	0.926	-1.200	2.431	0.506

None of the known risk factors summarized in table 4.12 had a significant association with amikacin trough levels.

4.8 Effects of aminoglycoside levels on renal function

Estimated glomerular filtration rate (eGFR) was calculated using the Schwartz equation and was classified according to the modified pRIFLE. The results were presented in table 4.17

Table 4.13: Aminoglycoside trough levels compared to the levels of kidney injury in pediatric patients admitted in KNH

Characteristic	No AKI	pRIFLE R	pRIFLE I
Gentamicin trough levels(mg/dl)			
Sub-therapeutic	49	3	8
Therapeutic	17	2	1
Supra-therapeutic	15	9	6
Total	81	14	15
Amikacin trough levels (mg/dl)			
Sub-therapeutic	15	2	4
Therapeutic	2	1	3
Supra-therapeutic	2	1	0
Total	19	4	7

Abbreviations: AKI, acute kidney injury; R, risk; I, Injury; F, failure; pRIFLE, pediatric RIFLE.

There was a significant reduction in glomerular filtration rate after treatment ($p < 0.001$) with a mean difference of 6.8 (95% C.I 2.0 to 11.7). On comparison of the eGFR before initiation of treatment and after treatment initiation there was a general decrease in renal function during therapy with some 19 (13.7%) showing a decrease of up-to 50%.

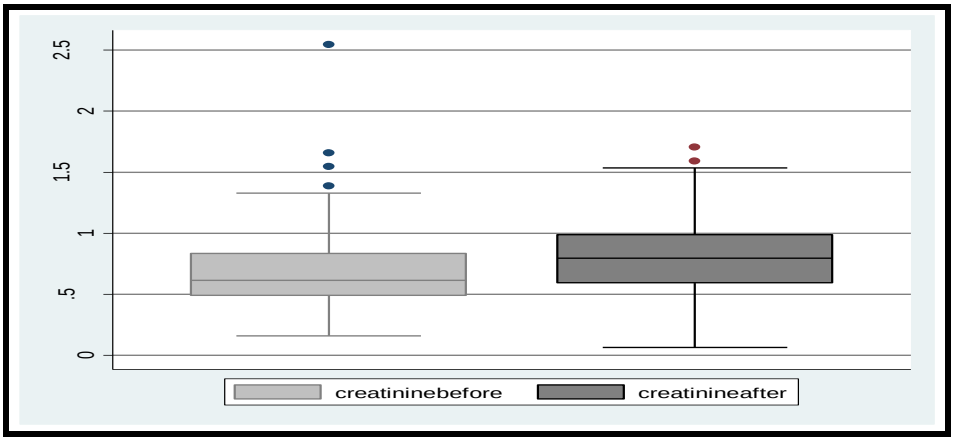

Figure 4.4: Effect of aminoglycosides on serum creatinine levels

Most participants showed a significant decrease in serum sodium ($p < 0.001$). Creatinine, urea and electrolyte levels have been found to be reliable indicators of kidney function. Kidney impairment causes a rise in serum creatinine and urea due to poor clearance by the kidney.

4.9 Hearing before and after medication administration

Echo- Screen TS Distortion product oto-acoustic emissions (DPOAE) instrument was used as a screening test for hearing loss before and after treatment with aminoglycosides. The equipment used presented two sounds of differing pitch and the ear generated a third pitch which was measured. The parameters measured included volume and the amount of time it took for the two tones to travel from the ear canal to the cochlea, generate a DPOAE and return the third tone back to the canal. Majority of the participants 139 (99%) in this study passed the screening test before and after drug administration. However, 1 (0.7%) participant showed hearing loss on the repeat test.

The participant was a male aged 15 months and weighed 10.9 kilograms. He was admitted for 17 days and was treated for pneumonia with amikacin 207 mg daily for a period of 7 days and he had a history of birth asphyxia, renal impairment and a history of having used 1-3 nephrotoxic and ototoxic medications. His amikacin trough level was 9.5 mg/L. He exhibited a reduction in serum sodium from 130 to 125 mEq/L and potassium levels from 4.3 to 3.2 mEq/L and an increase in serum creatinine. His eGFR reduced from 36.8 to 26.4 ml/min/1.73m^2. The incidence of hearing loss was 0.71%

CHAPTER FIVE: DISCUSSION

5.1 Aminoglycoside trough levels

Therapeutic drug monitoring is useful in monitoring both efficacy and toxicity. Elevated aminoglycoside trough levels suggest a reduced renal clearance of the aminoglycosides. In some instances, it may reflect a pre-existing renal impairment but it is also considered a risk factor for development of kidney injury (44). This study determined aminoglycoside levels and the proportion of the participants whose were above the therapeutic range was high in both gentamicin and amikacin. Pharmacokinetics and pharmacodynamics in young children is very different from that in adults. Protein binding, receptor function, end organ responsiveness, agonist and antagonist concentrations vary in children thus may lead to high serum trough levels (45).

When comparing the aminoglycoside trough levels obtained according to age in months and weight, it is evident that the highest mean trough concentration occurred in children 18 months and below and in those with weight less than 10 kgs. Very young children below the age of 18 months and those with a low weight need to be monitored closely to avoid toxicity.

5.2 Aminoglycoside induced acute kidney injury

Antimicrobials such as aminoglycosides are associated with acute kidney injury caused by allergic acute interstitial nephritis. These drugs can also cause a fluid and electrolyte imbalance. In this study there was a significant reduction in sodium and potassium levels which may be attributed to a defect in reabsorption of these ions in the proximal tubule which could have resulted in sodium and potassium wasting. A few case reports have reported such effects in patients treated with aminoglycosides. This phenomenon seemed to be associated with the duration of treatment and cumulative dose (high doses of aminoglycosides for periods longer than 6 days). This condition

was more likely to develop in patients who had a history of having used other nephrotoxic medication (46,47). Kidney function could be estimated by calculating the amount of creatinine that is cleared from the body by the kidneys. Serum urea and creatinine were also measured these are major indicators of kidney function. These are metabolic byproduct that could build up in blood if renal function is impaired. In this study there was a significant increase in serum urea and creatinine. A more precise measure of renal function is estimated Glomerular filtration rate (eGFR) which is a measure of creatinine clearance. Creatinine clearance in this study was estimated by using the Schwartz formula which used serum creatinine level, participants weight and age. Then the change in estimated glomerular filtration rate at baseline and after treatment was used to classify acute kidney injury (AKI) associated with aminoglycosides using the pediatric modified RIFLE criteria. There were 18 (12.9%) participants who were at risk of developing AKI and 19 (13.6%) who developed AKI. Some recent studies suggested that aminoglycoside induced AKI may occur in 20-30% of children exposed to aminoglycosides (44). However, some meta-analyses identified low incidences of nephrotoxicity with a RR 0.033, 95% CI: 0.12-0.89 while the Cochrane review did not find any nephrotoxicity (42).

5.3 Aminoglycoside induced hearing loss

Human studies show that aminoglycosides progressively accumulate in the inner ear and that the half-life of these drugs is 5-6 times that of plasma (48). It was also established that diffusion back to blood is dependent on the concentration of the drug in plasma and therefore ototoxicity was more likely to occur in patients with elevated plasma concentrations for long periods (48). However even a single dose could cause ototoxicity (48). By audiometry, it is estimated that 25% of patients on aminoglycoside treatment develop hearing loss (cochlear toxicity). However, studies published from 1991 to date show variable toxicity rates ranging from 0.9 – 25% (42). In this study

one participant showed hearing loss after treatment with an amikacin. He had amikacin trough level of 9.5 mg/L and this patient had a history of birth asphyxia. According to Schellack (49), conditions such as birth asphyxia can interfere with the aminoglycoside pharmacokinetics. The incidence of early hearing loss was 0.71%. Other studies that have been done in Africa show a wide variability in the incidence of aminoglycoside induced ototoxicity ranging from 7-90% (18). In a systematic review (50), which assessed 6 studies, the estimated incidence of hearing loss was 3% (95% CI 0-7) in neonates treated with gentamicin. Another study done on neonates who received amikacin showed a change in of the DPOAE of more than 2.4 dB from the base line but there was not a significant correlation between the DPOAE results and the trough levels due to a small sample size of 22 participants (28). The American Speech- Language – Hearing Association report that the true frequency of frequency of aminoglycoside induced hearing loss is unclear (18). Some of the factors that may contribute to variable estimates of ototoxicity include the differences in definition of otototoxicity, study designs and methodologies. Studies have also used different means to monitor for hearing. The sensitivity and specificity of DPOAE varied from 90-100% in different studies. The most recent study showed the DPOAE had a sensitivity of 97.6% and a specificity of 95.4% (51). We did not find any association between hearing loss and other known risk factors for hearing loss because the incidence was too low to allow for regression analysis.

Regression analysis between gentamicin trough levels and serum creatinine demonstrated a positive correlation. A study done on infants also did not find any association between hearing loss and a history of use of potentially nephrotoxic medication however it found a significant association between oxygen therapy and sensory neural hearing loss (52). Petersena and Rogersa identified patient characteristics such as a history of use of ototoxic medication and renal impairment as the risk factors for early hearing loss (53).

5.2 Strengths and Limitations of the study

This was a prospective cohort study thus the data was collected in real time and thus there was complete information. However, we used a smaller sample size of 140 instead of 147 thus this may affect the generalizability of the study findings. Replicate measurement of aminoglycoside trough levels was not done since we intended to determine that aminoglycosides were adequately eliminated and is not accumulating, we did a single measurement on the third day. Monitoring of trough levels alone is generally thought to be sufficient with the once daily dosing. We did not do Peak levels, since they are mainly measured in cases where individualized pharmacokinetic monitoring is required. we still faced a challenge when it came to testing for hearing loss because the wards were crowded thus the noise levels were high and the participants were very young children who could not stay calm during testing thus affecting the accuracy of the hearing tests. Neonates had low blood volumes therefore the small blood samples posed additional problems when doing kidney function tests as well as the trough levels. These factors may have contributed to the low aminoglycoside levels observed. To optimize dosing in pediatrics doses should adjusted based on the results of therapeutic drug monitoring.

In rare occasions, patient samples may contain heterophile antibodies which may have caused auto-agglutination of the microparticle reagent thus producing low results with this assay. This emphasizes the use of the patient's medical history together with other clinical examinations and other findings with the TDM results for diagnosis.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Aminoglycosides are widely used in pediatric patients admitted in KNH. These drugs have a narrow therapeutic index and could potentially result in acute kidney injury and irreversible hearing loss. The incidence of hearing loss and acute kidney injury in this study was low, However there was a high prevalence of trough levels in the sub therapeutic and supra-therapeutic ranges. Therefore there is need to review the existing aminoglycoside use protocols to include therapeutic drug monitoring and regular screening for hearing loss.

6.2 Recommendations for practice

1. Body surface area should be used to guide dosing.
2. A pharmacist should be attached in the pediatric wards to aid computation of aminoglycoside doses.

6.2.1 Recommendations for future research

1. Prospective studies with a large sample size would be recommended to determine the true incidence of ototoxicity because in this set up screening for hearing loss is not routinely done.
2. Further research in the utility of distortion product optoacoustic emissions a screening tests for early identification of hearing loss should be done in this setting.

3.11 Dissemination plan

The final thesis will be submitted to the Medical Library of the College of Health Sciences, University of Nairobi, for easy accessibility by the University students and staff.

The results of this study will be shared with Kenyatta National Hospital (KNH) through a CME which shall be organized by the respective hospital pharmacy departments. An abstract was submitted to the International Society of Pharmacoepidemiology (ISPE) and the Medicines Utilization Research in Africa Group (MURIA) and was accepted for poster presentation in both conferences and a manuscript will be published in a reputable journal.

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APPENDIX A: PARTICIPANT RECRUITMENT AND ELIGIBILITY CHECKLIST

A: WARD INFORMATION

Date	Ward	Number of new Admissions	Number of patients on aminoglycosides	Number of patients who meet the inclusion criteria	Number patients excluded

B: ELIGIBILITY CHECKLIST

1. **Age below 5 years** **yes** ☐ **No** ☐
2. **On aminoglycosides** **yes** ☐ **No** ☐
3. **Has birth asphyxia** **yes** ☐ **No** ☐
4. **Has congenital malformation** **yes** ☐ **No** ☐

APPENDIX B: INFORMED CONSENT FORM

Title of the study:

EVALUATION OF THE EFFECTS OF AMINOGLYCOSIDE TROUGH LEVELS ON THE RISK OF OTOTOXICITY AMONG PAEDIATRIC PATIENTS ADMITTED AT KENYATTA NATIONAL HOSPITAL

INSTITUTION	Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi P.O Box 30197-00400, Nairobi.
PRINCIPAL INVESTIGATOR	Dr. Zaietuni Akajoroit Mulaa P.O Box, 2672-30200, Kitale, Kenya. Phone number: 0718930391
SUPERVISORS	Dr. Margaret Oluka phone no. 0722604216 Email:olukamarga@yahoo.com Prof. Faith OKalebo Phone no. 0737434204 Email:okalebof@yahoo.com Dr. Sylvia Opanga Phone no. 0721296448 Email:sylvia.adisa@gmail.com
ETHICAL APPROVAL	Kenyatta National Hospital/University of Nairobi Ethical and Research Committee P.O Box 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102

Consent is requested from you to participate in this research study. The following principles will apply to all participants who choose to willingly participate. Your agreement to participate in this study is voluntary. You may withdraw at any point during the study without giving reasons for

withdrawal. After reading the study explains, please ask any questions which you feel will further enable you to understand the nature and the requirements of this study.

Introduction

My name is Dr. Zaietuni Akajoroit Mulaa; I am doing a study on aminoglycoside ototoxicity in children.

Aim of the study

This study is aimed at advocating for improved monitoring of patients through therapeutic drug monitoring and kidney function tests as well as audiometry in pediatric patients who are receiving aminoglycoside therapy.

Importance of the study

This study will be the basis for protocol and guideline development of aminoglycoside use which will help in dose calculation and monitoring of toxicity in pediatric patients who are admitted to the hospital in future.

Procedure to be followed

With your permission, we will obtain some background information from you and from the patients file then with your permission 2.0 ml of blood sample will be drawn by a qualified phlebotomist working in KNH before initiation of treatment to determine baseline creatinine levels and 2.0 ml of another sample will be collected from the patient after 72hours, 30minuites prior to the third dose of aminoglycoside determine plasma levels of the drug.

With your permission, a hearing test will be conducted on the first day of treatment and another Before discharge to determine if there is any early hearing loss.

Risks

Slight pain and discomfort at the injection site and possible excessive bleeding in patients with a bleeding disorder.

Benefits

Some of the data obtained will be used by the physician and clinical pharmacist in dosage calculation and adjustments for the individual patients and the research findings will also be used to develop treatment guideline in the Kenyatta National Hospital and possibly other hospitals in Kenya.

Assurance of confidentiality

All information you will provide will be kept confidentially. Your name will be coded and will not be mentioned or used at any point including any period during the study, data handling and during publications.

Contacts

In case of any concern and you need to contact me, my institution or Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee concerning this study kindly use the contacts provided. If in agreement, please sign the attached consent form

CERTIFICATE OF CONSENT

I have read and understood the information provided regarding the study and my questions regarding the study have been addressed. I willingly consent to participate in this study.

NAME OF PARTICIPANTS PARENT/GUARDIAN…….

SIGNATURE…… DATE……

Statement by the researcher:

I have provided all relevant information to the participant and I have answered all questions asked in regard to the study. I have explained to the Guardian that the participant's details will be recorded in a data collection form. Information collected will be provided voluntarily.

A copy of this informed consent has been provided to the participant.

NAME OF INVESTIGATOR ……

SIGNATURE…… DATE……

In case of any questions or concerns, feel free to contact any of the following:

The principal investigator Dr. Zaietuni Akajoroit Mulaa on 0718930391/0795022988
The lead supervisor Dr. Margaret Oluka on 0722604216
KNH/UON ethics committee on 2726300 ext 44102

APPENDIX C: DATA COLLECTING TOOL

APPENDIX D: COMEDICATION

Class of medication

SECTION I: PATIENT DEMOGRAPHIC DATA

1. Patient code#: _____

2. Ward#: _____

3. Sex: ☐Male ☐ Female

4. County of Residence:_____

5. Date of birth: __dd_/_mm__/__yr____

6. Gestational age _____ (weeks)

7. Age: _____☐ day☐ month☐ years

8. Admission Date: __dd_/_mm__/__yr____

9. Discharge Date: __dd_/_mm__/__yr____

10. Birth Weight: _____g

11. Current Weight: _____g

12. Height _____cm

SECTION II: RISK FACTOR INFORMATION

13. Was the participant born with any malformation? Yes ☐No ☐

14. Is there a family history of hearing loss in the family? Yes ☐ No ☐

15. Is the patient on an aminoglycoside? Yes ☐ No ☐

16. Does the patient already have an existing hearing problem? Yes☐ No ☐

17. Does the patient have a renal impairment? Yes ☐ No ☐

18. Does the patient have human immunodeficiency virus? Yes ☐ No ☐

SECTION III: INFORMATION FROM PATIENT FILE

19. Is the patient on an aminoglycoside? Yes ☐ No ☐

20. Has the patient been previously treated with an ototoxic medication? Yes☐ No ☐

a. Macrolides b. loop diuretics c. anti-neoplastic agents d. salicylates e. Quinine f. Other

21. Has the patient been treated with a nephrotoxic agent? Yes ☐No☐

a. Analgesics b. Antidepresants c. antihistamine d. Antimicrobials e. Diuretics f. Cardiovascular agents g. Chemotherapeutics h. Antiretrovirals i. Others

22. Is the patient on any other medication with potential for drug interaction? Yes☐ No ☐

If yes, what type of drug interaction?

It reduces elimination rate ☐ It increases elimination rate ☐

23. Does the participant have a history of birth asphyxia? Yes ☐ No ☐

DIAGNOSIS

24. What is the patient diagnosed with?

Sepsis ☐ Pneumonia ☐ Burns ☐ Menengitis ☐ Other _____

SECTION IV: LABORATORY PARAMETERS

25. What is the patient's Electrolyte urea creatinine (EUCs)

a. What are the patient's sodium levels?

Date				
Sodium levels				

b. What are the patient's potassium levels?

Date				
Potassium levels				

c. What are the patient's chloride levels?

Date				
Chloride levels				

d. What are the patient's urea levels?

Date				
Urea levels				

e. What are the patient's creatinine levels?

Date				
Creatinine levels				

26. What are the patient's trough levels?

Aminoglycoside	**Date started**	**Dose**	**frequency**	**Date stopped**	**duration**
gentamicin					

amikacin					

Aminoglycoside	**Date**	**time**	**Trough levels**
gentamicin			
amikacin			

27. What is the patients hearing status?

Test parameter	**Date of pre-treatment test**	**Pre-treatment Test result**	**Date of post-treatment test**	**Post-treatment Test result**

Entered by …… Signature……..

Checked by ……... Signature ……..

Analgesics

Ibuprofen

paracetamol

Antibiotics

Benzylpenicillin

Ceftriaxone

Ceftazidime

Other drugs

Frusemide

Meropenem

Oxygenation

Sildenafil

APPENDIX E: ETHICAL APPROVAL

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref. No.KNH/ERC/R/36

March 18, 2019

Dr. Zaietuni Akajoroit Mulaa
Reg. No.U51///87531/2016
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr. Mulaa

Re: Approval of Annual Renewal – Evaluation of the effects of aminoglycoside trough levels on the risk of ototoxity among paediatric patients admitted at Kenyatta National Hospital (P697/12/2017)

Refer to your communication dated February 20, 2019.

Upon review of your communication, the KNH-UON ERC hereby grants you annual extension approval for ethics research protocol **P697/12/2017**.

The approval dates are 19th March 2019 – 18th March 2020.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN- ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.

Protect to discover

g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

c.c. The Principal, College of Health Sciences, UoN
The Director CS, KNH
The Chairperson, KNH-UoN ERC
The Dean, School of Pharmacy, UON