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Clinical Pharmacokinetics of Amikacin in Neonates

*Gian Maria Pacifici[1], Giovanna Marchini[1]

[1] Via San Andrea 32, 56127 Pisa, Italy.

Abstract

Amikacin is a bactericidal aminoglycoside. Aminoglycosides inhibit bacterial protein synthesis. The antibacterial spectrum of amikacin is the broadest of aminoglycosides. Because of its resistance to many of the aminoglycosides-inactivating enzymes, it has a special role in hospitals where gentamicin- and tobramycin-resistant microorganisms are prevalent. Amikacin is active against the majority of aerobic gram-negative bacilli in the community and in the hospitals. This includes most strains of Serratia, Proteus, Enterobacter, and Escherichia coli that are resistant to gentamicin and tobramycin. Amikacin is active against Mycobacterium tuberculosis (99% of strains are inhibited by 4 µg/ml amikacin), including streptomycin-resistant strains atypical mycobacteria.

The gastrointestinal absorption of amikacin is minimal and is largely excreted through the renal glomerulus. In neonates, the dose of amikacin is 15 mg/kg. In the first week of life, a loading dose of 10 mg/kg followed by a maintenance regimen of 7.5 mg/kg has been suggested. After the first week of life, the corresponding doses are 17 mg/kg (loading dose) and 15 mg/kg (maintenance dose). The peak and trough doses of amikacin should be 20-30 µg/ml and <5 µg/ml, respectively. In neonates, the half-life of amikacin is 7 to 8 hours and in adults it is 1.3 hours. In infants, the half-life of amikacin inversely correlates with postnatal age and body weight. Amikacin therapeutic serum concentrations are not ototoxic and nephrotoxic in term neonates. The aim of this study is to review the clinical pharmacology of amikacin in term neonates.

Key Words: Amikacin, Effects, Neonate, Pharmacokinetics.

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Corresponding Author:

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacificigm@tiscali.it

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1-INTRODUCTION

The aminoglycoside antibiotics are rapidly bactericidal. The higher the concentration, the greater is the rate at which bacteria are killed. Aminoglycosides inhibit bacterial protein synthesis. All bind to sites on the 30S subunit of the bacterial ribosome, causing an alteration in the codon: anticodon recognition. This results in misreading of the messenger RNA and hence in the production of defective bacterial proteins. Their penetration through the cell membrane of the bacterium depends partly on oxygen-dependent active transport by a polyamine carrier system and they have minimal action against organisms. Their affect is bactericidal and is enhanced by agents that interfere with cell wall synthesis (1).

Aminoglycosides diffuse through aqueous channels formed by porin proteins in the outer membrane of gram-negative bacteria to enter the periplasmic space. Amikacin is an aminoglycoside antibiotic. The spectrum of antimicrobial of amikacin is the broadest of aminoglycosides. Because of its resistance to many of the aminoglycosides-inactivating enzymes, it has a special role in hospitals where gentamicin and tobramycin-resistant microorganisms are prevalent. Amikacin is the preferred agent for the initial treatment of serious nosocomial gram-negative bacillary infections. Amikacin is active against the majority of aerobic gram-negative bacilli in the community and in the hospital. This includes most strains of Serratia, Proteus, and Enterobacter, and Escherichia coli that are resistant to gentamicin and tobramycin. Most resistance to amikacin is found among strains of Pseudomonas other than Pseudomonas aeruginosa. Amikacin is active against Mycobacterium tuberculosis (99% of strains are inhibited by 4 µg/ml), including streptomycin-resistant strains atypical mycobacteria (2).

Amikacin is a semi-synthetic aminoglycoside antibiotic first developed in 1972. It can be particularly useful in the treatment of gram-negative bacteria resistant to gentamicin (such as certain Enterobacter species). Significant placental transfer occurs and, although the drug has not been documented as causing fetal damage, it would seem wise to monitor blood levels when amikacin is used in pregnancy to minimize the risk of fetal ototoxicity because drug accumulation has been documented in fetal lung, kidney and placenta. Only small amounts of amikacin appear in human milk, and the absorption from the gut is minimal, the breastfed infant is unlikely to suffer from adverse effects.

Amikacin is largely excreted through the renal glomerulus. The half-life is 7-14 hours in neonates with a postmenstrual age of less than 30 weeks and 4-7 hours at a postmenstrual age of 40 weeks. The adult half-life is 1.3 hours. Nephrotoxicity and cochlear or vestibular damage can occur if the trough blood levels in excess of those recommended go uncorrected as with all aminoglycosides. The risk is increased if amikacin is prescribed at the same time as a diuretic such as furosemide. The risk is increased if amikacin is prescribed for more than 10 days (3).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, EMBASE, Google scholar and PubMed as search engines; November 2016 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

The following key words "amikacin pharmacokinetics neonate", "amikacin effects neonate", "amikacin dosage neonate", "amikacin toxicity neonate" and

"amikacin resistance neonate", were used to search for the relevant literature. In addition, the books Neonatal Formulary (3) and NEOFAX by Young and Mangum (4) were consulted.

3-RESULTS

3-1. Treatment

Give 15 mg/kg intravenously or intramuscularly to infants less than 4 weeks and 20 mg/kg to infants older than this (3).

3-2. Blood levels

The trough level is all that usually needs to be monitored in infants on high-dose treatment once every 24-36 hours, and this is probably only necessary as a routine in infants less than 10 days old or with possible renal failure. Aim for a trough level of less than 5 µg/ml. The 1 hour peak level, when measured should be 20-30 µg/ml (3).

3-3. Uses

Restricted to treatment of infections caused by gram-negative bacilli that are resistant to other aminoglycosides. Usually used in combination with a β-lactam antibiotic (4).

3-4. Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentrations 30 min after the end of infusion, and trough concentration just prior to the next dose. When treating infants with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible. Peak should be 20-30 mg/l (or Cmax/MIC ratio greater than 8:1). Trough concentrations should be 2-5 µg/ml (4).

3-5. Amikacin dosage regimens in neonates

Four neonates with normal renal function who were given amikacin 7.5 mg/kg 12 hourly intramuscularly had unsatisfactory levels (peak 9.45$\pm$3.6, trough 1.23$\pm$1.69 µg/ml). The loading dose of 10 mg/kg followed by the above regime did not improve levels in two more neonates (peaks 7.8 and 12 µg/ml, troughs 0.4 and 2.4 µg/ml, respectively). Satisfactory levels were achieved in 14 other neonates with normal renal function with a new regime of 10 mg/kg 12 hourly (peak 21.5$\pm$4.5 µg/ml, trough 3.34$\pm$2.05 µg/ml). In two other neonates weight loss resulted in a higher dose being given inadvertently (> 11.5 mg/kg 12 hourly), and excessively high levels were achieved (peak 35$\pm$8 µg/ml, trough 8.2$\pm$2.0 µg/ml) (5). In neonates with normal renal function, the postnatal age ($r = 0.43$, p-level = 0.01), and weight ($r = 0.49$, p-level = 0.005) correlated with half-life.

In a retrospective analysis, outcomes of amikacin therapy were evaluated in two groups of Korean neonates: group 1 (n = 107), who received amikacin according to standard neonatal dosing recommendations and empirical dosing guidelines, which often resulted in a need for dosage adjustment; and group 2 (n = 74), who were treated under a revised dosage regimen derived from pharmacokinetic data on group 1 and taking into account unusually high interindividual variability in amikacin clearance among Korean newborns relative to Caucasian populations (6). The influences of post-conceptional and postnatal age on amikacin pharmacokinetics were also evaluated. Relative to standard and empirical amikacin dosing, the revised dosage regimen resulted in a significantly higher percentage of neonates achieving peak concentrations within the target range of 20-30 µg/ml (81.3% in group 2 versus 50.7% in group 1, p-level = 0.001). The

percentage of neonates with a peak concentration of <20 µg/ml was significantly lower in group 2 (3.8%) versus group 1 (21.6%, p-level<0.001), as was the proportion of neonates with peak concentrations of > 30 µg/ml (15.0% versus 27.6%, p-level < 0.001), and the need for dosage adjustment by a pharmacist (31.6% versus 59.7%, p-level = 0.056). A new amikacin dosing regimen based on the pharmacokinetic parameters of Korean neonates was effective in achieving peak and trough amikacin concentrations within the target range.

Berger et al. (7), developed a simplified amikacin dosage regimen for nosocomial infections in preterm infants including a loading dose in order to achieve therapeutic maximum serum concentrations early in the course of therapy. The modified amikacin dosing and monitoring protocol included a loading dose of 10 mg/kg in the first week of life, followed by a maintenance regimen of 7.5 mg/kg every 24 hours. After the first week of life the corresponding doses were 17 mg/kg (loading) and 15 mg/kg (maintenance). A peak level was measured 30 min after the second dose, and a trough level was measured immediately before the third dose. Twenty-five very low birth-weight infants (median birth-weight 739 grams, median gestational age 25 weeks), who had 34 episodes of amikacin treatment were included in the analysis.

Median amikacin peak and trough were 37.1 µM and 6.3 µM, respectively. Twenty-nine of all peak levels (85%) and 30 of all trough levels (88%) were within the targeted range > 35 µM and < 8.5 µM, respectively. All neonates with elevated trough levels were of extremely low birth-weight and were born in the 24th week of pregnancy. Hearing evaluations were performed in 17 of 19 surviving infants at discharge home, all of which gave normal results. The new amikacin dosing protocol yielded targeted peak and trough concentrations in a high percentage of very low birth-weight infants with nosocomial infection after the first week of life. This simplified dosage regimen achieved acceptable serum concentrations in all birth-weight and gestational age groups, with the exception of extremely low birth-weight infants weighing less than 700 grams and/or with a gestational age of 24 weeks or less.

The pharmacokinetics of amikacin administered intravenously at currently recommended doses (7.5 mg/kg every 12 hours for infants with less than 7 days of life; 7.5 mg/kg every 8 hours for infants with greater than 7 days of life), were studied in 28 preterm infants weighing less than 2,500 grams (mean$\pm$ standard deviation [SD], 1,380$\pm$470 grams; post-conceptional age, 30.50$\pm$2.86 weeks) (8). The medication was infused over 45 min. Trough and peak serum samples as well as two additional samples were taken at steady-state. The results showed a statistically significant relationship between half-life (8.42$\pm$2.55 hours), and post-conceptional age (p-level=0.02). These pharmacokinetic data were used to calculate a new dosage schedule for preterm infants. The derived intravenous dosage of amikacin for infants of less than 30 weeks of post-conceptional age was 9 mg/kg every 18 hours. For infants of greater than 30 weeks of post-conceptional age, the dosage was 9 mg/kg every 12 hours. Peak and trough levels of amikacin in serum that fell within the therapeutic range were compared by using the currently recommended dosage schedule and the dosage schedule derived from the pharmacokinetic data by Kenyon et al. (8). There was a reduction in the number of peak and trough levels that fell outside the accepted therapeutic range which was not statistically significant. Extension of the dosing interval and a further increase in the dosage may result in further improvement. Based on these data, the

current recommendations are inadequate for preterm infants. The derived dosage schedule of Kenyon et al. (8) improved, but did not eliminate high trough and low peak levels of amikacin in all infants. Sherwin et al. (9) examined the pharmacokinetics of amikacin and their pharmacodynamic relations in neonates to develop an alternative dosing strategy for amikacin in neonates. A population pharmacokinetic/pharmacodynamic analysis was performed using data collected from 80 neonates with gestational ages from 24 to 41 weeks. Simulation of a new dosing regimen yielded the following recommendations: 15 mg/kg at 36 hours intervals, 14 mg/kg at 24 hours intervals and 15 mg/kg at 24 hours interval for neonates ≤ 28 weeks, 29-36 weeks and ≥ 37 weeks post-menstrual age, respectively.

The recommended doses (7.5-10 mg/kg loading; 15 mg/kg in two divided doses administered intravenously), were given to 5 infants with body weight ≤ 1,000 grams and 13 larger infants (10). Trough levels 11.5 hours after a dose were 16.6±11.9 µg/ml in infants with body weight ≤ 1,000 grams and 6.5±4.3 µg/ml in larger infants (p-level < 0.02), were observed. Peak levels one hour post-infusion exceed 40 µg/ml in 3 of 5 infants with body weight ≤ 1,000 grams and 4 of 12 infants with body weight > 1,000 grams (not statistically significant). Overall, 7 of 10 peak and/or trough levels of amikacin in infants with body weight ≤ 1,000 grams were in the range considered toxic in adults, versus 7 of 24 in larger infants (p-level = 0.03). These data show that surprisingly excessive blood levels of amikacin are likely in infants with body weight ≤ 1,000 grams, and may also occur in larger infants using currently recommended dosage schedules. A marked change in the pharmacokinetics of amikacin has been reported during neonatal life. Amikacin has a very narrow therapeutic range and can cause very serious side effects such as nephrotoxicity and ototoxicity (11). The current therapeutic dose of amikacin, i.e. 15 mg/kg, may increase the risk of toxicity in preterm infants with immature renal function. Siddiqi et al. (11) aimed to determine the frequency of amikacin toxicity in preterm infants as compared to term infants by measuring its serum trough levels following the administration of the current therapeutic dose.

A total of 104 infants (52 term neonates, with a gestational age of 37-40 weeks, and 52 preterm neonates, with a gestational age of 29-36 weeks), receiving amikacin at a dose of 15 mg/kg, once daily, for bacterial infection were enrolled. Amikacin trough levels were measured at 72 hours of therapy. The preterm infants had significantly higher median (range) 11.33 (1.50-42.60) µg/ml levels of serum amikacin as compared to 8.5 (2.8-33.0) µg/ml levels of serum amikacin in term infants (p-level is <0.001). The preterm infants had a high frequency of toxic 32 (62%) and subtherapeuic 12 (23%) levels, as compared to 11 (21%) and 5 (10%) in term infants, respectively. Serum amikacin levels revealed a positive correlation with post-dose serum creatinine (r=0.48; p-level < 0.05). The current practice of amikacin treatment for bacterial infection needs to be adjusted due to unique pharmacokinetic variability in preterm infants. There is a need for regular therapeutic drug monitoring and renal function assessment in all infants receiving amikacin therapy in order to avoid nephrotoxicity.

3-6. Once versus twice daily dosing of amikacin in neonates

Kotze et al. (12) compared the potentially toxic effects in full term neonates of amikacin administered once daily, versus amikacin administered twice daily. A controlled, randomized, prospective study was performed in which one group of full term neonates received amikacin 15 mg/kg per dose once daily (n=20), and the other

received amikacin 7.5 mg/kg per dose twice daily (n=20). Impairments of renal on glomerular function was defined as a decline of less than 50% of the expected physiological drop in serum creatinine over time. Brainstem auditory evoked potentials were also evaluated and amikacin blood levels taken. Fifteen neonates in the once-daily group and 12 neonates in the twice-daily group demonstrated at least one period of renal function impairment while in hospital. This decreased to 5 of 16 and 4 of 16 during follow-up. These differences were not statistically different. Brainstem auditory evoked potentials did not find signs of ototoxicity at any time. In full term neonatal patients, once daily dosing of amikacin is no more toxic than the twice daily regimen.

Abdel-Hady et al. (13) compared the efficacy and safety (nephrotoxicity) of once daily versus twice daily dosing of amikacin in neonates with suspected or proven sepsis and reported on the drug's pharmacokinetics in these neonates. Thirty neonates of gestational age ≥ 36 weeks and body weight ≥ 2,500 grams with suspected or proven sepsis were randomized to receive amikacin either at a dose of 15 mg/kg once per day (group 1, n=15), or a dose of 7.5 mg/kg twice per day (group 2, n=15). Amikacin was infused over 1 hour. Peak and trough serum samples for amikacin were measured for all infants at steady-state. Nephrotoxicity was assessed by serum creatinine and urinary N-acetyl-beta-D-glucosaminidase before and at 7 days of therapy. Clinical efficacy was compared using both observation of clinical status and normalization of laboratory tests. All neonates in group 1 achieved a trough levels > 10 µg/ml and 2 neonates had trough concentration > 10 µg/ml in group 2. No significant difference was found between group 1 and group 2 in either baseline or day 7 of treatment in the creatinine serum concentration. No significant difference was found between the two groups in clinical efficacy or renal toxicity. The calculated pharmacokinetic parameters were in group 1 and group 2, respectively: clearance 63.9±15.9 ml/kg/h and 73.5±18.1 ml/kg/h; the distribution volume was 0.54±0.09 l/kg and 0.73.5±1.0 l/kg, and the half-life was 6.1±1.0 hours and 5.95±1.1 hours. Amikacin given once every 24 hours to septic neonates of ≥ 36 weeks of gestation achieved higher peak levels and lower trough concentrations than the twice daily regimen. Treatment with once daily regimen did not lead to more nephrotoxicity than with a twice-daily regimen, and showed comparable efficacy.

Guadalupe Vasquez-Mendoza et al. (14) assessed the efficacy and renal toxicity of one daily dose of amikacin versus several doses in infected full term newborn infants. A clinical trial was conducted with 120 neonates who were divided into two groups: group A (n=60), infants who received amikacin 20 mg/kg per day in one dose; and group B (n=60) infants who received amikacin 10 mg/kg every 12 hours. Both groups also received ampicillin 100 mg/kg per day. Blood levels of amikacin, urinary beta (2)-microglobulin, serum creatinine concentration, and glomerular filtration rate were measured in each neonate. No significant difference was found in demographic characteristics as well as in their beta (2)-microglobulin, serum creatinine, and glomerular filtration rate levels in the two groups. Infection was resolved in 96% for infants of group A and 91% in group B (p-level=0.254). Renal toxicity was present in 20.0 versus 31.6%, respectively (p-level=0.211). In both groups no significant difference was found in peak amikacin levels, whereas trough levels were higher in group B (p-level=0.004). No significant difference was found in efficacy or renal toxicity in either groups. These authors recommend

using amikacin in one daily dose. It could diminish the manipulation of intravenous access, reducing the risk of nosocomial infections.

3-7. Effects of amikacin in neonates

Poblano et al. (15) described whether there are some relationships between amikacin serum levels and central conduction time in brainstem auditory evoked potential within therapeutic range levels in newborns as an index of drug toxicity in brainstem auditory centers in neonatally exposed infancy. These authors performed a cross-sectional study to compare brainstem evocated potentials from 35 infants under amikacin administration and 24 control infants; both examinations were blinded to investigators. Bivariate and partial correlations were calculated between amikacin and brainstem auditory evoked potential measured in treated infants. Amikacin determinations were within therapeutic concentrations. No clinical alterations in the brainstem auditory evoked potential were found and no differences between amikacin-treated and control infants were found. Significant positive Pearson correlation between latency of III-V and I-V interweave intervals and amikacin Cmin serum levels was found and was present when calculations were controlled by partial correlations for gestational age at birth and Apgar score at 5 min. The present findings suggest that increased amikacin levels are related to increased latencies in III-V and I-V interweave intervals among infants, which may be an early index of brainstem effects of subclinical neurotoxicity.

Amikacin clearance has recently been proposed as a marker of renal maturation in neonates. Zhao et al. (16) performed an explanatory study to evaluate the predictive performance of a renal maturation model derived from amikacin to predict on glomerular filtration rate and vancomycin clearance in neonates. The study was based on a cohort of 116 neonates using non-linear mixed-effects modeling NONMEM software. There was a good correlation between predicted and observed glomerular filtration rate and vancomycin clearance in neonates. The prediction error is not significantly correlated with age. An amikacin maturation model can precisely reflect maturation of glomerular filtration and thus predict the dosage regimen of other renally excreted drugs by glomerular filtration in neonates. The square of the correlation coefficient, and means of the prediction error (2.5th-97.5th percentiles) and absolute prediction error (2.5th-97.5th percentiles) are 0.96, 1.2 % (-39.7 to 30.0 %) and 12.3 % (0.4-39.7 %), respectively, for Glomerular filtration rate (GFR), and 0.97, -11.3 % (-38.2 to 15.4 %) and 14.0 % (0.5-38.2%), respectively, for vancomycin. The prediction error is not significantly correlated with age. An amikacin maturation model can precisely reflect maturation of glomerular filtration and thus predict the dosage regimens of other renally excreted drugs by glomerular filtration in neonates.

Studies in adults have indicated that phospholipiduria is rapidly increased during aminoglycoside therapy. Ibrahim et al. (17) studied the effects of amikacin on phospholipiduria in male prematurity-born neonates (gestational age > 34 weeks; postnatal age ≤ 2 days) by assessing the urinary excretion of 4 enzymes (N-acetyl-beta-D-glucosaminidase, alkaline phosphatase, tauglutamyltransferase and alanine aminopeptidase), and 4 low-molecular-weight proteins (Beta 2-Microglobulin, clara cell protein, microalbumin and retinol-binding protein), which are currently used to monitor the development and extent of renal tubular damage. Twenty-two patients and 8 healthy (as control) neonates were enrolled in the study. Patients were treated with amikacin (15 mg per day) given in one dose (n=10) or two equal injections (b.i.d.,

n=12) for duration of 7-11 days. Phospholipiduria and proteinuria were determined in 24-hours urine sample collections, and enzymes were assessed in spot urine collected at 9 A.M. Ibrahim et al. (17) found that in neonates, amikacin causes a significant increase in phospholipiduria, and in enzymuria except for N-acetyl-beta-D-glucosamine in the qb group. Proteinuria showed no significant change due to amikacin treatment. No significant differences were observed between one dose and 2 times a day (b.i.d) administration of amikacin for all parameters tested. These authors conclude that phospholipiduria could be used in neonates as well as in adults as a non-invasive method to monitor the development of the renal phospholipidosis during aminoglycoside therapy.

3-8. Resistance to amikacin in neonates

An outbreak of amikacin-resistant Enterobacteriacae occurred in intensive care nursery (18). Epidemic disease and an increased colonization rate in newborn infants due to amikacin-resistance microorganisms has not been documented previously. Three of the 11 neonates died. The microorganisms had not been documented previously. Three microorganisms isolated were resistant to amikacin and two experimental aminoglycosides, sissomicin and netilmicin. The outbreak was contained following the institution of several control measures, including pharyngeal inoculation of an experimental strain of α-streptococcus in four infants.

Two multiresistance Klebsiella pneumoniae strains isolated from cerebrospinal fluid of human neonates were analyzed for their plasmid content (19). Two of the plasmids harbored by these strains, pJHCMW1 (11 kilobase pairs) and pJHCMW4 (75 kilobase pairs) carried genetic determinants for amikacin resistance. These plasmids also encoded to kanamycin, tobramycin, and ampicillin which could be transferred to Escherichia coli by conjugation. Extracts from transconjugant derivatives carrying pJHCMW4 produced an acetyltransferase activity that acetylated all three aminoglycosides. Transconjugant derivatives carrying pJHCMW1 encoded both acetylating and phosphorylating activities. Southern blot hybridization analysis indicated considerable DNA homology between these two plasmids.
Escherichia coli is the leading cause of various infections, both in community and nosocomial settings. Ferjani et al. (20) determined the antibiotic resistance rates and the phylogenetic groups of invasive Escherichia coli and assessed the relationship between these characteristics according to the community or nosocomial origin of the strains. One hundred non-redundant Escherichia coli strains, causing invasive infections were collected and investigated between 2010 and 2012. The phylogenetic groups were determined by triplex Polymerase chain reaction (PCR).

The statistical analysis was performed with Pearson x2 test and p-levels < 0.05 were considered as statistically significant. Sixty-three strains were community-acquired and 37 were hospital-acquired (20). The resistance rates among community-acquired and hospital-acquired were respectively: cefotaxime (11.1/37.8%), ciprofloxacin (19/43.2%), amikacin (3.2/27.2%), and cotrimoxazole (42.8/64.8%). Escherichia coli strains caused bacteremia (community-acquired=34.9%; hospital-acquired=83.7%), peritonitis (community-acquired=58.7%; hospital-acquired=13.5%), appendicitis (community-acquired=3.2%; hospital-acquired=2.7%), and cholecystitis (community-acquired=32%/0%).

The distribution of phylogenetic groups among community-acquired and hospital-acquired stains: A (25.4/18.9), B1 (9.5/16.2%), B2 (23.8/37.8%), and D

group (41.3/27.3%). High resistance rates to cefotaxime (p-level = 0.02), ciprofloxacin (p-level = 0.01, amikacin (p-level = 0.001), and cotrimoxazole (p = 0.05), were statistically significantly associated with a nosocomial origin. These results prove the diversity of phylogroups among Escherichia coli invasive strains whatever their origin, and a higher antibiotic resistance rate in nosocomial strains. An adequate use of antibiotics and applying strict hygiene measures would limit the transmission and selections of these bacteria in hospital as well as in community settings.

Gram-negative isolates from blood and cerebrospinal fluid were monitored for 1 year before and 1 year after the first-line aminoglycoside in a busy pediatric department was changed from gentamicin to amikacin (21). In the general pediatric wards, the switch to amikacin resulted in no change resistance of nosocomial gram-negative infections to either amikacin (0% before and after) or gentamicin (23.9 [before] versus 26.5% [after]). In the neonatal unit, the switch to amikacin was followed by an outbreak of Serratia species that were commonly resistant to amikacin, but susceptible to gentamicin. This outbreak abated spontaneously. In the year after the change in aminoglycoside usage, the resistance to amikacin of nosocomially acquired gram-negative bacilli increased from 7.6 to 27.7% (p-level<0.001), and the resistance to gentamicin decreased from 71.2 to 60.2% (p-level=0.07). The increase in amikacin resistance of gram-negative bacilli other than Serratia species has persisted for more than one year after the introduction of amikacin as the sole aminoglycoside. The different effects observed in the two sections of the pediatric department may be related to the more intensive usage of aminoglycoside in the neonatal unit.

A prospective study was conducted to determine the prevalence of aminoglycoside-resistant Staphylococcus aureus and coagulase-negative staphylococci before and after the introduction of amikacin as the sole aminoglycoside used in the burn unit of the adult of the intensive care unit, and neonatal intensive care unit (22).

Pharyngeal or endotracheal cultures, as well as superficial surveillance cultures, were collected weekly during the following four study periods: all units for 4 months before amikacin introduction, all units 4 to 8 months after, all units 12 to 13 months after, and the neonatal intensive care units 30 months after. A total of 2,613 strains of coagulase-negative staphylococci and 316 strains of Staphylococci aureus were obtained from 916 patients. During the course of the study, amikacin-resistant coagulase-negative staphylococci increased from 0 to 22%, colonizing 43% of patients, whereas no amikacin-resistant Staphylococcus aureus was detected. During the course of the study, amikacin-resistant coagulase-negative staphylococci increased from 0 to 22%. During the pre-amikacin survey, 68% of the coagulase-negative staphylococci and 12% of Staphylococcus aureus strains were resistant to tobramycin and gentamicin. This resistance did not decrease after amikacin was introduced. Initially, 83% of the aminoglycoside-resistant coagulase-negative staphylococci were resistant to both tobramycin and gentamicin. During the last surveillance this value dropped to 40%, and 48% of the strains had become resistant to all three aminoglycosides. Resistance to aminoglycosides, including amikacin, develops quickly in coagulase-negative staphylococci from clinical areas where these antimicrobial agents are widely used. However, aminoglycoside resistance in Staphylococcus aureus is much less frequent.

Because of the increased aminoglycoside resistance of hospital bacterial isolates,

aminoglycoside sensitivity patterns of isolates in a large children's hospital were assessed before and during a 33-month period of almost exclusive amikacin use (23). There was no significant change in overall resistance rates of gram-negative enteric bacteria to gentamicin (4.8% and 4.6%), tobramycin (2.5% and 3.6%), and amikacin (1.2% and 1.8%) from the pre-amikacin period to the amikacin usage period, respectively. No significant differences were observed for isolates of Escherichia coli, Klebsiella, Serratia, Acinetobacter, and Pseudomonas species.

In contrast, significant decreases in gentamicin and tobramycin resistance rates for Enterobacter, Citrobacter, and Pseudomonas aeruginosa and in gentamicin resistance of Proteus were found. Very little change in resistance of staphylococcal isolates was seen during a shorter evaluation period. Pediatric aminoglycoside usage includes therapy of neonatal infections, cystic fibrosis, febrile neutropenic episodes in patients with cancer abdominal surgery, bacterial endocarditis, and gram-negative central system infections. Amikacin has also been used successfully as single-dose therapy of urinary tract infections, and acceptable cerebrospinal fluid levels of amikacin have been documented in hydrocephalic patients with ventriculitis. In vitro studies of 22 bacterial isolates demonstrated synergy between amikacin and penicillin or newer cephalosporins in 13, and additive effect in seven and indifference in two. No antagonism was found in addition. In addition, in vivo synergy between imipenem and amikacin was found in neutropenic infant radioallergosorbent test (RAST) with Pseudomonas aeruginosa sepsis using a strain with which no synergy was demonstrated in vitro. Because excessive or inadequate level are frequent with usually recommended doses, particularly in neonates and patients with compromised renal function or cystic fibrosis, serum levels should be monitored to minimize risk and to ensure therapeutic levels.

3-9. Treatment of neonatal infections with amikacin

A total of 3,959 infants were admitted to the neonatal intensive care unit and 2,385 infants (60%) received 2,791 courses of aminoglycoside therapy (24). Aminoglycoside use totaled 16,279 infant days of which 16,070 (98.7%) were with amikacin. A total of 1,017 pairs of pre- and post-treatment endotracheal or pharyngeal specimens yielded 318 gram-negative bacteria isolates. Gram-negative bacteria were isolated from 381 clinical specimens. Of the 318 surveillance and 380 clinical isolates tested, 285 (90%) and 358 (94%), respectively, were susceptible to amikacin.

Amikacin resistance did not increase during the study. Amikacin-resistant microorganisms were isolated more frequently from infants receiving multiple courses than those receiving single courses of amikacin and resistant microorganisms were not usually found before the administration of amikacin. None of the 15 amikacin-resistant isolated made 6'-N-aminoglycoside acetyltransferase and 3 isolates took up only small amounts of radiolabeled amikacin, suggesting that resistance was due to decreased permeability. The extensive use of amikacin in a neonatal intensive care unit for over 5 years did not result in an increase of amikacin-resistant gram-negative bacteria.

Amikacin was used in the treatment of various gram-negative infections in 66 children ranging in age from 2 days and 13 years (25). Over 72% of the infections treated were classified as severe and the remaining were moderate. Among infections in which the site of origin was the urinary or gastro-intestinal tract, amikacin achieved 38 (95%) complete or partial cured 6 (75%) out of 8 patients. The

remaining 18 infections involved skin, soft tissue and other miscellaneous categories in which amikacin therapy resulted in 17 (94%) complete or partial cures. Overall, amikacin achieved 54 complete cures and seven clinical or bacteriological cures in 76 patients, which represents an 82% complete cure rate and 10% partial cure rate for all the patients studied.

Thirty (86%) of 35 infants and older children with proven gram-negative sepsis had a complete clinical remission after treatment with amikacin (26). In 27 (82%) of 33 infectious episodes for which bacteriologic results were available before and after treatment, the microorganism was eradicated. The dosage of amikacin was either 7.5 mg/kg or 15 mg/kg given intramuscularly at 12-hours intervals. No adverse clinical effects or laboratory abnormalities were observed during treatment, which lasted from 5 to 14 days. All bacteria were sensitive to amikacin when tested by the disk diffusion method, but a single strain of Pseudomonas was sensitive when tested by the agar dilution method. Assays of serum and urine demonstrated adequate levels of amikacin after single intramuscular injection of 3.75 or 7.5 mg/kg; simultaneous assays of serum and cerebrospinal fluid in two cases demonstrated comparable concentrations of drug suggestive of a high degree of penetration into the cerebrospinal fluid during infection. Serial measurements of amikacin in serum ranged from 0.5 to 12 hours after administration of single doses of 7.5 mg/kg of amikacin to six newborns revealed no significant differences in the concentrations achieved with intramuscular or intravenous administration of the drug.

3-10. Pharmacokinetics of amikacin in neonates

Amikacin clearance has recently been proposed as a marker of renal maturation in neonates. Zhao et al. (16) presented an explanatory to evaluate the predictive performance of renal maturation models derived from amikacin to predict the glomerular filtration rate and vancomycin clearance in neonate. A total of 116 neonates were studied using non-linear mixed-effects modeling NONMEM softwares. Zhao et al. (16) demonstrated good correlations between predicted and observed glomerular filtration rate and vancomycin clearance in neonates. The square of the correlation coefficient, and means of the prediction error (2.5th-97.5th percentiles), and absolute prediction error (2.5th-97.5th percentiles) are 0.96, 1.2 % (-39.7 to 30.0 %) and 12.3 % (0.4-39.7 %), respectively, for GFR, and 0.97, -11.3 % (-38.2 to 15.4 %) and 14.0 % (0.5-38.2 %), respectively, for vancomycin. The prediction error was not significantly correlated with age. An amikacin maturation model can precisely reflect maturation of glomerular filtration and thus predict the dosage regimens of other renally excreted drugs by glomerular filtration in neonates.

Intrauterine growth restriction and prematurity are associated with a low nephron endowment (27). It can therefore be expected that neonates who are born prematurely and/or after intrauterine growth retardation have a lower glomerular filtration rate. Schreuder et al. (27), hypothesized that amikacin clearance is lower after intrauterine growth restriction or prematurity birth as a marker of low nephron endowment. Amikacin clearance was retrospectively analyzed in 191 neonates who received amikacin within the first 24-hours of life. These authors showed that birth z- score and gestational age are correlated with the clearance of amikacin (partial correlation coefficient 0.159, p-level = 0.046, and 0.396, p-level < 0.001, respectively), after correction for other factors. Renal clearance on the first day of life was lower in neonates with a lower gestational age and/or birth weight z- score. This indicates

that both prematurity and intrauterine growth restriction impair the glomerular filtration rate on the first day of life.

Padovani et al. (28) studied 32 neonates who were treated with amikacin for suspected or documented bacterial infection. Nineteen neonates were preterm (mean gestational age was 32.0±3.6 weeks, mean body weight was 1,740±820 grams), while the remaining 13 infants were full-term (mean body weight was 3,190±820 grams). The 32 neonates were given amikacin by intramuscular route. To estimate amikacin pharmacokinetic parameters, the serum concentration values of amikacin were fitted to the one-compartment pharmacokinetic model. The kinetic parameters of amikacin are summarized in **Table.1**.

The intraindividual variability of amikacin pharmacokinetics was evaluated by the standard two-stage method yielding an interindividual variability coefficient of 28.9%. No previous estimate of this parameter has yet been published. The population parameters of amikacin in neonates, derived from the study by Padovani et al. (1993) (i.e. coefficient for intraindividual variability and mean ± SD for clearance and distribution volume), can be applied to a further series of neonates to facilitate the prospective use of the bayesian method for individualizing amikacin dosage.

Vucicevic et al. (29) compared the peak and trough amikacin concentrations after twice-daily or once-daily dosing in full-term neonates. Additionally, the authors aimed to address amikacin pharmacokinetics and its variability. Data included infants born on term. Amikacin daily dose was 15 or 20 mg/kg depending on the neonate's age. Infants randomly received amikacin every 12 or 24 hours. In all infants corresponding peak and trough were taken. The mean peak of 21.79 µg/ml in the twice daily group was statistically different from peak of 36.39 µg/ml in the once-daily group. Average trough in the twice-daily group (6.67 µg/ml) was statistically different from the corresponding 3.99 µg/ml in the once-daily group. The kinetic parameters of amikacin are summarized in **Table.1**.

High interindividual pharmacokinetic variability was observed. Neonatal age contributed to the pharmacokinetic parameter values. Statistical significant difference in clearance and half-life was observed between infant age ≤ 2 and >2 days of therapy initiation. As expected, amikacin once-daily dosing achieved higher peak and lower trough concentrations than twice-daily dosing. Based on the results, observed variability in amikacin pharmacokinetics was possibly due to the renal maturation process. Twenty-nine neonates of different gestational ages with confirmed or suspected infections due to gram-negative bacteria were given amikacin at an average dose of 7.2 mg/kg every 12 hours (30).

The treatment was started during the first or second day of life and stopped when neonates were 7.6±2.5 days old. The range of gestational ages was 28.5-42 weeks (mean±SD = 34.5±3.3 weeks) and birth weights ranged from 900 to 4,500 grams (mean±SD = 1,980±920 grams). Trough concentrations of amikacin were monitored during the treatment, on cessation of therapy, the disappearance of amikacin was followed in plasma samples taken by heel puncture (50 µl) at 30 min, 1, 2, 3, 6, and 12 hours and then daily as long as the concentrations of amikacin were measurable. The pharmacokinetic parameters of amikacin are summarized in **Table.1**.

After the last administration of amikacin, this drug decay was measured in plasma and urine for 100-250 hours. The serum concentration versus time profiles were fitted by nonlinear regression analysis. The parameters of a 2 or 3-compartmment model with elimination from the central

compartment were calculated. Initial elimination half-life, distribution volume of the central compartment, and steady state distribution volume were significantly related to intrauterine maturation whereas no significant linear correlation was found between clearance and postnatal age (r = 0.19).

Patients with gestational age less than 34 weeks had a significantly reduced clearance when compared with the neonates with gestational age greater than 36 weeks had (0.78±0.17 versus 1.0±0.4 ml/h/kg, p-level<0.05). The ratio between the volumes of distribution showed that a higher amount of amikacin penetrates the peripheral compartments with increased gestational age. The renal clearance calculated in six infants averaged 66% of the total body clearance, suggesting that elimination of the drug can occur in the neonate via non-renal routes. Analysis of the long term urinary elimination of amikacin showed that about 5% of the total amount of the drug administered in 5-8 days of treatment is retained in the organism. Although quantitatively small, this amount is relevant for the potential nephrotoxicity of the drug.

Smits et al. (31) studied the prospective evaluation of a pharmacokinetic model of amikacin dosing regimen. First, early (before and after second dose) therapeutic drug monitoring observations were evaluated for achieving target trough (< 3 µg/ml) and peak (> 24 µg/ml) levels. Second, all observed therapeutic drug administration concentrations were compared with model-predicted concentrations, whereby the results of a normalized prediction distribution error were considered. Subsequently, Monte Carlo simulations were performed. Finally, remaining causes limiting amikacin predictability (i.e., prescription errors and disease characteristic outliers) were explored. In 579 neonates (median birth weight, 2,285 grams, medial postnatal age 2 days, median gestational age 34 weeks), 90.5% of the observed early peak levels reached 24 µg/ml, and 60.2% of the trough levels were < 3 µg/ml (93.4% ≤ 5 µg/ml). Observations were accurately predicted by the model without bias, which was confirmed by normalized prediction distribution error. Monte Carlo simulations showed that peak concentrations > 24 µg/ml were reached at steady-state in almost all patients. Trough values < 3 µg/ml at steady-state were documented in 78% to 100% and 45% to 96% of simulated cases with and without ibuprofen administration, respectively; suboptimal trough levels were found in patients with postnatal age < 14 days and current weight of > 2,000 grams. Prospectively evaluation of a model-based neonatal amikacin dosing regimen resulted in optimized resulted peak and trough concentrations in almost all patients. Slightly adapted dosing for patient subgroup with suboptimal trough levels was proposed. This model-based approach improves neonatal individualizing.

3-11. Therapeutic amikacin serum concentrations are not ototoxic and nephrotoxic in term neonates

The hearing function was assessed by Distortion Product Otoacustic Emission in neonates. No relationship between amikacin serum trough concentration and ototoxicity in neonates with neonatal sepsis was observed (32).

Abdel-Hady et al. (13) administered 15 mg/kg once per day (group 1) or 7.5 mg/kg twice per day (group 2), to neonates with gestational age ≥ 36 weeks. No significant difference was found between the two groups in either baseline or day 7 serum creatinine serum concentration. No significant difference was found between the two groups in renal toxicity. Poblano et al. (15) administered amikacin to 35 newborns and 24 infants who had not received amikacin. These authors described whether there are some

relationships between amikacin serum levels and central conduction time in brainstem auditory evocated potentials within therapeutic range levels of amikacin in newborns as index of drug toxicity. Amikacin serum concentrations were within therapeutic levels. No clinical alterations in brainstem auditory evocated potentials were found. No differences between amikacin-treated and control infants were found.

Sixty full-term infants received 20 mg/kg per day of amikacin and 60 infants received 10 mg/kg amikacin every 12 hours. Blood levels of amikacin, urinary beta (2)-microglobulin, serum creatinine and glomerular filtration rate were measured in each patient. No significant difference was found in renal toxicity in either groups (14). Langhendries et al. (33) assessed the tolerance of the once-a-day administration of amikacin in comparison with the twice daily dose regimen, amikacin 15 mg/kg per day quaque die (q.d) (n=10) or b.i.d. (n=12).

Glomerular dysfunction was assessed by creatinine clearance, and tubular injuries by urinary excretion of proteins (retinol binding protein, alkaline phosphate, alanine aminotransferase, and Gamma-glutamyltransferase, and total phospholipids in urine). Ototoxicity was assessed by brainstem auditory evoked potentials at 0, 3 and 9 days of therapy. Eight healthy neonates served as controls. Brainstem auditory evoked potentials at day 9 were not significantly different between treated infants and controls.

Table-1: Pharmacokinetic parameters of amikacin in neonates

Gestational age (weeks)	Body weight (grams)	Number of cases	Half-life (hours)	Daily dose (mg/kg)	Clearance (ml/h/kg)	Distribution volume (l/kg)	Reference
Preterm and term	3.19±0.82	32	7.6±4.4	15 IM	64.6±30.8	0.65±0.414	28
≥ 37	NA	31	6.8±2.5	15 - 20 IM	86.9±48.2	0.78±0.38	29
34.5±3.3	1980±920	29	6.8±2.9	7.2 x 2 IV	51.6±17.4	0.80±0.23	30
≥ 30	≥ 2,500	15	6.1±1.0	15 IV	63.9±15.9	0.54±0.09	13
≥ 30	≥ 2,500	7.5 x 2	5.9±1.1	7.5 x 2 IV	73.5±18.1	0.61±0.13	13
Adults	NA	NA	1.3±0.6	15 IV	78.0±36	0.27±0.06	34

IM = Intramuscularly; IV = Intravenously; NA: Not available.

4-DISCUSSION

Amikacin is an aminoglycoside antibiotic. Among the aminoglycosides, amikacin has the broadest spectrum of antimicrobial activity (2). Amikacin is resistant to many of the aminoglycosides-inactivating enzymes and it has a special role in hospitals where gentamicin and tobramycin-resistant microorganisms are prevalent. Amikacin is active against the vast majority of aerobic gram-negative

bacilli in the community and hospitals. This includes most strains of Serratia, Proteus, and P. aeruginosa. It is active against nearly all strains of Klebsiella, Enterobacter, and Escherichia coli that are resistant to gentamicin and tobramycin. Most resistance to amikacin is found among strains of Acinetobacter, Providencia. Amikacin is not active against the majority of gram-positive anaerobic bacteria. It is active against mycobacterium tuberculosis (99% of strains are inhibited by 4 µg/ml) (2).

The daily dose of amikacin is 15 mg/kg administered intravenously or intramuscularly to infants less than 4 weeks and 20 mg/kg to infants older than this the peak and trough concentrations should be 20-30 µg/ml and less than 5 µg/ml, respectively. Serum concentrations should be monitored when treating for more than 48 hours (3). Cookson et al. (5) suggested administering amikacin at the dosage of 10 mg/kg every 12 hours followed by a maintenance dose of 7.5 mg/kg every 24 hours. These authors observed that the amikacin half-life significantly (p-level = 0.01) correlates with postnatal age and body weight.

Berger et al. (7) developed a simplified amikacin dosage regimen for nosocomial infections in preterm infants including a loading dose. The loading dose is 10 mg/kg in the first week of life, followed by a maintenance regimen of 7.5 mg/kg every 24 hours. After the first week of life, the daily doses of amikacin are 17 mg/kg (loading) and 15 mg/kg (maintenance). Median amikacin peak and trough concentrations were 37.1 µg/ml and 6.3 µg/kg, respectively. Median amikacin peak and trough were 37.1 µM and 6.3 µM, respectively. Kenyon et al. (8) administered amikacin intravenously at the dosage of 7.5 mg/kg every 12 hours in infants with less than 7 days of life and 7.8 mg/kg amikacin every 8 hours for infants with greater age than 7 days of life. The infants (n=28) weighed 1,380±470 grams and the post-conceptional age was 30.52±2.86 weeks. A statistically significant relationship (p-level = 0.02) was observed between post-conceptional age and amikacin half-life of 8.42±2.55 hours. The intravenous dosage of amikacin for infants of less than 30 weeks of post-conceptional age are 9 mg/kg every 18 hours. For infants of greater than 30 weeks of post-conceptional age, the dosage of amikacin was 9 mg/kg every 12 hours. The derived dosage schedule of Kenyon et al. (8) did not eliminate high trough and low peak levels of amikacin in all infants.

Simulation of a new dosage regimen of amikacin was developed by Sherwin et al. (9) in 80 neonates with gestational ages from 24 and 41 weeks. The dosage regimens were 15 mg/kg at 36 hours intervals, 14 mg/kg at 24 hours intervals and 15 mg/kg at 24 hours intervals for neonates ≤ 28 weeks, 29-36 weeks and ≥ 37 weeks post-menstrual age, respectively. Philips et al. (10) measured the trough and peak concentrations of amikacin in 5 infants with body weight ≤ 1,000 grams and 13 larger infants. Amikacin doses were 7.5-10 mg/kg loading; 15 mg/kg in two divided doses administered intravenously every 24 hours. The trough levels were 16.6±11.9 µg/ml in infants with body weight ≤ 1,000 grams and 6.5±4.3 µg/ml in larger infants (p-level < 0.02). Peak levels exceed 40 µg/ml in 3 of the 5 infants with body weight ≤ 1,000 grams and 4 of 12 infants with body weight > 1,000 grams. Overall, 7 of 10 peaks and/or trough levels of amikacin in infants with body weight ≤ 1,000 grams were in the range considered toxic in adults, versus 7 of 24 in larger infants (p-level = 0.03).

Amikacin has a very narrow therapeutic range and can cause very serious side effects such as nephrotoxicity and ototoxicity (11). The amikacin dose of 15 mg/kg, may increase the risk of toxicity in

preterm infants with immature renal function. Infants (n=52) with a gestational age of 37-40 weeks and infants (n=52) with a gestational age of 29-36 weeks received a daily dose of 15 mg/kg. Amikacin concentrations were measured at 72 hours after the initiation of therapy. The preterm infants had significantly higher median trough serum concentrations of amikacin (11.33 µg/ml) as compared to 8.5 µg/ml serum levels of amikacin in term infants (p-level < 0.001). The preterm infants had a high frequency of toxic (62%) and subtherapeutic (23%) levels, as compared to (21%) and (10%) in term infants, respectively. Serum amikacin levels correlated with post-dose serum creatinine (r = 0.48; p-level value <0.005).

Kotze et al. (12) compared the potentially toxic effects in term neonates who received amikacin administered once daily, versus amikacin administered twice daily. Twenty infants received amikacin 15 mg/kg once daily and other 20 infants received amikacin 7.5 mg/kg twice daily. Fifteen neonates in the once-daily group and 12 neonates in the twice-daily group demonstrated at least one period of renal function impairment while in hospital. In full term neonatal infants, once daily dosing amikacin is no more toxic than the twice daily regimen.

Fifteen infants with a body weight ≥ 2,500 grams received 15 mg/kg amikacin intravenously once per day (group 1) or a dose of 7.5 mg/kg twice per day (n=15; group 2). Clinical efficacy was compared using both observation and normalization of laboratory tests (13). All neonates in group 1 achieved trough levels of amikacin > 10 µg/ml and 2 neonates had trough amikacin concentration > 10 µg/ml in group 2. No significant difference was found between group 1 and 2 in either baseline or day 7 of treatment in the creatinine serum concentration. No significant difference was found between the two groups in clinical efficacy or renal toxicity. Amikacin given once every 24 hours to septic neonates of ≥ 36 weeks of gestation achieved higher peak levels and lower trough concentrations than the twice daily regimen. Treatment with once daily regimen did not lead to more nephrotoxicity than with a twice-daily regimen, and showed comparable efficacy. Sixty infected term neonates received amikacin 20 mg/kg per (group A) and other sixty infected term neonates received 10 mg/kg amikacin every 12 hours (14). Infection was resolved in 96% for infants of group A and 91% for group B (p-level = 0.254). Renal toxicity was present in 20 infants versus 31.6 infants, respectively (p-level = 0.211). In both groups no significant difference was found in peak amikacin levels, whereas trough levels were higher for group B (p-level = 0.004). These authors recommend using amikacin in one daily dose.

Poblano et al. (15) observed that there are not clinical alterations in the brainstem auditory evocated potential in neonates treated with amikacin. Zhao et al. (16) proposed amikacin clearance as a marker of renal maturation in neonates. The study was based on a cohort of 116 neonates using non-linear mixed-effects modeling NONMEM software. An amikacin maturation model can precisely reflect maturation of glomerular filtration rate and thus predict the dosage regimen of other renally excreted drugs by glomerular filtration in neonates.

Ibrahim et al. (17) studied the effects of amikacin on phospholipiduria in 22 premature neonates by assessing the urinary excretion of 4 enzymes (N-acetyl-beta-D-glucosaminidase, alkaline phosphatase, tauglutamyltransferase and alanine aminopeptidase), and 4 low-molecular-weight proteins (beta [2]-microglutamin, clara cell protein and retinol-binding protein). Infants received 15 mg amikacin intravenously per day given in one dose (n=10), or two equal

injections (n=12) for the duration of 7-11 days. Ibrahim et al. (17) found that in neonates, amikacin causes a significant increase in phospholipiduria, and enzymuria except for N-acetyl-beta-D-glucosamine. No significant differences were observed between the two regimens of amikacin. These authors conclude that phospholipiduria could be used in neonates as a non-invasive method to monitor the development of the renal phospholipidosis during aminoglycoside therapy.

Escherichia coli is the leading cause of various infections, both in community and nosocomial settings (20). Escherichia coli strains caused bacteremia (community-acquired = 34.9%; hospital-acquired = 83.7%), peritonitis (community-acquired = 58.7%; hospital-acquired = 13.5%), appendicitis (community-acquired = 3.2%; hospital-acquired = 2.7%), and Cholecystitis (community-acquired = 32%). High resistance rates to cefotaxime (p-level = 0.02), ciprofloxacin (p-level = 0.01), amikacin (p-level = 0.001), and cotrimoxazole (p-level = 0.05), were statistically significantly associated with a nosocomial origin. These results prove the diversity of phylogroups among Escherichia coli invasive strains whatever their origin, and a higher antibiotic resistance rate in nosocomial strains.

Gram-negative isolates from blood and cerebrospinal fluid were monitored for 1 year before and 1 year after the first-line aminoglycoside (21). The switch to amikacin resulted in no change resistance of nosocomial gram-negative infections to either amikacin (0% before and after) or gentamicin [23.9%] before versus 26.5% [after]. In the year after the change in aminoglycoside usage, the resistance to amikacin of nosocomially acquired gram-negative bacilli increased from 7.6 to 27.7% (p-level <0.001), and the resistance to gentamicin decreased from to 71.2 to 60.2% (p-level = 0.07). The increase in amikacin resistance of gram-negative bacilli other than Serratia species persisted for more than 1 year after the introduction of amikacin as the sole aminoglycoside. The prevalence of aminoglycoside-resistant Staphylococcus aureus and coagulase-negative staphylococci before and after the introduction of amikacin as the sole aminoglycoside was studied by Hammerberg et al. (22) in a neonatal intensive care unit. A total of 2,613 strains of coagulase-negative staphylococci and 316 strains of Staphylococci aureus were obtained from 916 infants. The amikacin-resistant coagulase-negative staphylococci increased from 0 to 22%, colonizing 43% of infants whereas no amikacin-resistant Staphylococcus aureus was detected. During the pre-amikacin survey, 68% of the coagulase-negative staphylococci and 12% of Staphylococcus aureus strains were resistant to tobramycin and gentamicin. Resistance to aminoglycosides, including amikacin, develops quickly in coagulase-negative staphylococci from clinical areas where these antimicrobial agents are widely used.

The resistance to aminoglycosides was assessed before and during a 33-month period of almost exclusive amikacin use (23). There was no significant change in overall resistance rates of gram-negative enteric bacteria to gentamicin (4.8% and 4.6%), tobramycin (2.5% and 3.6%), and amikacin (1.2% and 1.8%) from the pre-amikacin period to the amikacin usage period, respectively. No significant differences were observed for isolates of Escherichia coli, Klebsiella, Serratia, Acinetobacter, and Pseudomonas species. Amikacin has also been used successfully as single-dose therapy of urinary tract infections, and acceptable cerebrospinal fluid levels of amikacin have been documented in hydrocephalic patients with ventriculitis. A total of 3,959 infants were admitted to the neonatal intensive care unit and 2,385 infants (60%) received 2,791 courses of aminoglycoside therapy ([24).

Aminoglycoside use totaled 16,279 infant days of which 16,070 (98.7%) were with amikacin. Gram-negative bacteria were isolated from 381 clinical specimens. Of the 318 surveillance and 380 clinical isolates tested 285 (90%) and 358 (94%), respectively, were susceptible to amikacin. Amikacin resistance did not increase during the study. Amikacin-resistant microorganisms were isolated more frequently from infants receiving multiple courses than those receiving single courses of amikacin and resistant microorganisms were not usually found before the administration of amikacin. The extensive use of amikacin in a neonatal intensive care unit for over 5 years did not result in an increase of amikacin-resistant gram-negative bacteria.

Amikacin was used in the treatment of various gram-negative infections in 66 children ranging in age from 2 days and 13 years (25). Over 72% of the infections treated were classified as severe and the remaining were moderate. Among infections in which the site of origin was the urinary or gastro-intestinal tract, amikacin achieved 38 (95%) complete or partial cures in forty patients. In respiratory tract infections, amikacin completely or partially cured six (75%) out of eight patients. The remaining eighteen infections involved skin, soft tissue and other miscellaneous categories in which amikacin therapy resulted in seventeen (94%) complete or partial cures. Overall, amikacin achieved fifty-four complete cures and seven clinical or bacteriological cures in sixty-six patients, which represents an 82% complete cure rate and 10% partial cure rate for all the patients in the study. Thirty (86%) of 35 infants and older children with proven gram-negative sepsis had a complete clinical remission after treatment with amikacin (26). In 27 (82%) of 33 infectious episodes for which bacteriologic results were available before and after treatment, the microorganism was eradicated. The dosage of amikacin was either 7.5 or 15 mg/kg given intramuscularly at 12-hours intervals. The pharmacokinetic parameters of amikacin in neonates are summarized in table 1. The half-life of amikacin ranges between 5.9$\pm$1.1 and 7.6$\pm$4.4 hours in neonates and is 1.3$\pm$0.6 hours in adults. The clearance of amikacin ranges between 51.6$\pm$17.4 and 86.9$\pm$48.2 ml/h/kg in neonates and is 78.0$\pm$36 ml/h/kg in adults. The distribution volume ranges between 0.54$\pm$0.09 and 0.80$\pm$0.23 l/kg in neonates and is 0.27$\pm$0.06 l/kg in adults. Zhao et al. (16) demonstrated good correlations between predicted and observed glomerular filtration rate and vancomycin clearance in neonates. An amikacin maturation model can precisely reflect maturation of glomerular filtration rate and thus predicts the dosage regimens of other renally excreted drugs by glomerular filtration in neonates.

Intrauterine growth restriction and prematurity are associated with a low nephron endowment (27). Neonates who are born prematurely and/or after intrauterine growth retardation have a lower glomerular filtration rate. Schreuder et al. (27) hypothesized that amikacin clearance is lower after intrauterine growth restriction or prematurity birth as a marker of low nephron endowment. These authors showed that birth z- score and gestational age are correlated with the clearance of amikacin. Renal clearance on the first day of life is lower in neonates with a lower gestational age and/or birth z- score.

Padovani et al. (28) studied 32 neonates who were treated with amikacin. Nineteen neonates were preterm while the remaining 13 infants were full-term. The interindividual variability of amikacin pharmacokinetics was evaluated by the standard two-stage method yielding an interindividual variability coefficient of 28.9%. Vucicevic et al. (29) compared peak and trough amikacin concentrations

after twice-daily or once-daily dosing in full-term neonates. Amikacin daily dose was 15 or 20 mg/kg depending on the neonate's age. Mean peak of 21.79 µg/ml in the twice daily group was statistically different from peak of 36.39 µg/ml in the once-daily group. Average trough in twice-daily group (6.67 µg/ml) was statistically different from the corresponding 3.99 µg/ml in the once-daily group. High interindividual pharmacokinetic variability was observed. Statistical significant difference in clearance and half-life was observed between infant age ≤ 2 and > days of therapy. Observed variability in amikacin pharmacokinetics may be due to the renal maturation process.

Amikacin (7.2 mg/kg) was given every 12 hours to neonates of different gestational ages (30). The treatment was started during the first or second day of life and stopped when neonates were 7.6±2.5 days old. Trough concentrations of amikacin were monitored during treatment, on cessation of therapy. The serum concentration of amikacin versus time profiles were fitted by nonlinear regression analysis. Initial elimination half-life, distribution volume of the central compartment, and steady-state distribution volume were significantly related to intrauterine maturation whereas no significant linear correlation was found between clearance and postnatal age (r=0.19). Infants with gestational age less than 34 weeks had a significantly reduced clearance when compared with the neonates with gestational age greater than 36 weeks (p-level <0.05).

A higher amount of amikacin penetrates the peripheral comportments with increased gestational age. The renal clearance calculated in six infants averaged 66% of the total body clearance, suggesting that elimination of amikacin can occur in the neonate via non-renal routes. Before and after the second dose of amikacin the therapeutic drug monitoring observations were evaluated for achieving target trough (< 3 µg/ml) and peak (> 24 µg/ml) levels (31). Monte Carlo simulations were performed. In 579 neonates, 90.5% of the observed early peak levels reached 24 µg/ml, and 60.2% of the trough levels were < 3 µg/ml (93.4% ≤ 5 µg/ml). Monte Carlo simulations showed that peak concentrations > 24 µg/ml were reached at steady-state in almost all infants. Trough values < 3 µg/ml at steady-state were documented in 78% to100% and 45% to 96% of simulated cases with and without ibuprofen administration, respectively; suboptimal trough levels were found in patients with postnatal age 14 days and current body weight of > 2,000 grams.

No relationship between amikacin serum trough concentrations and ototoxicity was observed (32). Abdel-Hady et al. (13) administered amikacin 15 mg/kg once per day (group 1) or 7.5 mg/kg twice per day (group 2) to neonates with gestational age ≥ 36 weeks. No significant difference was found between the two groups in either baseline or day 7 serum creatinine concentrations. No significant difference was found between the two groups in renal toxicity. Poblano et al. (15) observed that amikacin did not cause alterations in brainstem evoked potentials. Guadalupe Vasquez-Mendoza (14) administered amikacin (20 mg/kg per day) to 60 infants and another 60 infants received 10 mg/kg amikacin every 12 hours. No significant difference was found in renal toxicity in either groups. Langhendries et al. (33) administered amikacin 15 mg/kg per day. Ototoxicity was assessed by brainstem auditory evoked potentials at day 9 of therapy and was not significantly different between treated infants and controls.

5- CONCLUSION

In conclusion, amikacin is a bactericidal aminoglycoside. The antibacterial spectrum of amikacin is the broadest of

aminoglycosides. Amikacin is active against the majority of aerobic gram-negative bacilli in the community and in hospitals. Amikacin is active against most strains of Serratia, Proteus, Enterobacter, Escherichia coli, and Mycobacterium tuberculosis. Amikacin is resistant to many of the aminoglycosides-inactivating enzymes. In the first week of life, a loading dose of 10 mg/kg is followed by a daily maintenance dose of 7.5 mg/kg. Amikacin may be administered 15 mg/kg once a day or two doses of 7.5 mg/kg at intervals of 12 hours. No clinical alterations in the brainstem evoked potentials were observed after administration of amikacin to term neonates. In neonates, the half-life ranged between 5.9 and 7.6 hours and in adults it is 1.3 hours. Therapeutic amikacin serum concentrations are not ototoxic and nephrotoxic in term neonates.

6- CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

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