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Clinical Pharmacology of amikacin in infants and children

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Abstract

Amikacin spectrum of activity is the broadest of all aminoglycosides. Amikacin is active against most strains of Serratia, Proteus, and Pseudomonas aeruginosa as well as most strains of Klebsiella, Enterobacter, and Escherichia coli that are resistant to gentamicin and tobramycin and is rapidly bactericidal. Amikacin doses are 15 mg/kg once-daily, and 7.5 mg/kg twice-daily in infants, and 20 to 40 mg/kg once-daily in children. Amikacin is preferentially administered once-daily, because yields lower though and higher peak concentrations, thus reducing the risks of toxicity, and increases peak concentration, thus improving therapeutic efficacy. Amikacin is absorbed rapidly after intramuscular injection; its peak plasma concentration is 20 μg/ml after an injection of 7.5 mg/kg. Amikacin mean half-lives are 6.0 hours in infants in the first weeks of life, and 1.9 hours in children aged up to 6 years. Amikacin causes limited ototoxicity and nephrotoxicity in infants and children. After a single intramuscular amikacin dose of 7.5 mg/kg, its concentration (μg/ml) is 14.9 in serum, 2.2 in skeletal muscle, and 1.9 in fat tissue. Because of its polar nature, amikacin penetrates poorly into the cerebrospinal fluid, and serum peak to amniotic fluid ratio is 0.03. Amikacin pharmacokinetics have been extensively studied in infants and children and pharmacokinetic parameters vary remarkably. Half-life and clearance decreases and increases, respectively, during infant maturation. Burn, cancer and renal impairment have an important impact on pharmacokinetics. Some bacteria may become resistant to amikacin. The aim of this study is to review the published data on amikacin effects, metabolism, pharmacokinetics, and bacteria-resistance in infants and children.

Introduction

Amikacin can be particularly useful in the treatment of gram-negative bacteria resistant to gentamicin and tobramycin such as certain Enterobacter species. Significant placental transfer occurs but the drug does not cause foetal damage. It would seem wise to monitor blood levels when amikacin is used in pregnancy to minimise the risk of foetal ototoxicity because drug accumulation has been documented in the foetal lung, kidney and placenta. Only small amounts appear in human milk, and as absorption from the gut is minimal, the breastfed infant is unlikely to suffer from adverse effects. Amikacin is largely excreted through the renal glomerulus. Elimination half-lives are 7 to 14 hours in infants, with a post-menstrual age of less than 30 weeks, and 4 to 7 hours at a postmenstrual age of 40 weeks. Nephrotoxicity and cochlear or vestibular damage can occur if 'trough' blood levels are in excess of those generally recommended. The risk is increased if amikacin is prescribed for more than 10 days, follows treatment with another aminoglycoside, or is given at the same time as a diuretic such as furosemide. Amikacin is less toxic to the neonatal kidney than gentamicin or netilmicin, and also probably less ototoxic. Absorption is said to be somewhat unpredictable after intramuscular administration in very small infants. Cerebrospinal fluid penetration is limited [1].

Measure serum concentrations when amikacin is administered for more than 48 hours. Obtain peak concentration 30 min after the end of infusion, and trough concentration just prior to the next dose. When treating infants with serious infections measure serum concentration 24 hours after a dose. The Cmax/MIC ratio should be greater than 8:1. Dosing recommendations are based on: (1) higher peak concentrations increase concentration-dependent bacterial killing. (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic. (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Distribution volume is increased and clearance is decreased in infants with patent ductus arteriosus. Serum elimination half-life is prolonged in premature and asphyxiated infants. Inactivation of amikacin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-depended process. This is probably clinically significant only when penicillin-containing compounds are mixed in intravenous solutions or when the blood is at room temperature for several hours before the assay is performed. Amikacin is incompatible with fat emulsion, amphotericin B, ampicillin, azithromycin, heparin (concentrations > 1 unit/ml), imipenem/cilastatin, mezlocillin, nafcillin, oxacillin, phenytoin, propofol, thiopental, and ticarcillin/clavulanate [2].

The spectrum of amikacin activity is the broadest of all aminoglycosides. Because of its resistance to many of the aminoglycoside-inactivating enzymes, amikacin has a special role for the initial treatment of serious nosocomial gram-negative bacillary infections in hospitals where resistance to gentamicin and tobramycin has become a significant problem. Amikacin is active against most strains of Serratia, Proteus, and Pseudomonas aeruginosa as well as most strains of Klebsiella, Enterobacter, and Escherichia coli that are resistant to gentamicin and tobramycin. Most resistance to amikacin is found amongst strains of Acinetobacter, Providencia, and Flavobacterium and strains of Pseudomonas other than Pseudomonas aeruginosa; these all are unusual pathogens. Amikacin is not active against the majority of gram-positive anaerobic bacteria. It is active against Mycobacterium tuberculosis, including streptomycin-resistant strains, and atypical mycobacteria. The recommended dose of amikacin is 15 mg/kg daily

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as a single dose or divided into two or three equal portions, which must be reduced for patients with renal failure. Amikacin is absorbed rapidly after intramuscular injection, and peak concentrations in plasma approximate 20 μg/ml after injection of 7.5 mg/kg. The concentration, 12 hours after a 7.5 mg/kg dose, is 5 to 10 μg/ml. A 15-mg/kg once-daily dose produces peak concentrations of 50 to 60 μg/ml and a trough concentration < 1 μg/ml. Aminoglycosides frequently are used in combination with a cell wall-active agents (β-lactam or glycopeptides) for the therapy of serious proven or suspected bacterial infections. The three rationales for this approach are: (1) to expand the empiric spectrum of activity of the antimicrobial regimen, (2) to provide synergistic bacterial killing, and (3) to prevent the emergence of resistance to the individual agents. As with the other aminoglycosides, amikacin causes ototoxicity, hearing loss, and nephrotoxicity [3]. For treatment of mycobacterial infections, thrice-weekly dosing schedule is used, with doses up to 25 mg/kg [4].

Because of their polar nature, aminoglycosides do not penetrate well into most cells, the central nervous system, or the eye. The apparent distribution volume of aminoglycosides is 25% of lean body-weight and approximates the volume of extracellular fluid. The aminoglycosides distribute poorly into adipose tissue, which must be considered when weight-based dosing regimens in obese patients. Concentrations of aminoglycosides in secretions and tissue are low [5]. High concentrations are found only in the renal cortex, endolymph and perilymph of the inner ear; the high concentration in these sites likely contributes to the nephrotoxicity and ototoxicity caused by these drugs. As a result of active hepatic secretion, concentrations in the bile approach 30% of those found in plasma, but this represents a very minor excretory route for aminoglycosides. Inflammation increases the penetration of aminoglycosides into peritoneal and pericardial cavities. Concentrations of aminoglycosides achieved in the central nervous fluid with parenteral administration are usually subtherapeutic [6]. Treatment of meningitis with intravenous administration is generally suboptimal. Intrathecal or intraventricular administration of aminoglycosides has been used to achieve therapeutic level in this central nervous system but the availability of expanded-spectrum cephalosporins has generally made this unnecessary [3].

Literature search

The literature search was performed electronically using PubMed database as search engine, the cut-off point was November 2019. The following key words: "amikacin infants effects", "amikacin children effects", "amikacin infants metabolism", "amikacin children metabolism", "amikacin infants pharmacokinetics", "amikacin children pharmacokinetics", "amikacin infants resistance", and "amikacin children resistance" were used. In addition, the books Neonatal Formulary [1] and NEOFAX by Young and Mangum [2] were consulted.

Results

Administration schedule of amikacin in infants and children

Treatment of infants with amikacin: give 15 mg/kg intravenously or intramuscularly to infants < 4 weeks old and 20 mg/kg to infants > this. Give a dose every 36 hours in infants less than 28 weeks gestation in the first week of life. Give all other infants a dose once-daily unless renal function is poor. Check the trough serum level just before the fourth dose is due and increase the dosing regimen interval if this level is > 5 μg/ml [1].

Check blood levels in infants: the trough level is all that usually needs to be monitored in infants on high-dose treatment once every 24 to 36 hours, and this is probably only necessary as a routine in infants < 10 days old or with possible renal failure. Aim for a trough level of < 5 μg/ml. The 1 hour peak level should be 20 to 30 μg/ml [1].

Treatment of children with amikacin: the suggested dose is 20 mg/kg once-daily in children aged 5.5 months to 13 years [7].

Amikacin efficacy and safety in children

A double-blind, randomized clinical trial of the efficacy and safety of once-daily dose versus a multiple daily doses amikacin therapy was conducted for children, aged 2 to 12 years, with an intraoperative diagnosis of perforated appendicitis [8]. One-hundred children were randomized following a one-to-one randomization to receive either amikacin 7.5 mg/kg trice-daily or 22.5 mg/kg once-daily. Efficacy was evaluated by the occurrence of intra-abdominal abscesses or therapeutic failure. Safety was determined by the presence of renal or cochlear toxicity, between the multiple daily doses and once-daily dose. Amikacin was found to be safe and effective in both therapeutic dosing regimens.

The efficacy and safety of an amikacin 20 mg/kg dose once-daily intravenously infused for 7 to 19 consecutive days, to children suffering from fever and granulocytopenia, undergoing bone marrow transplantation [9]. Amikacin peak serum concentrations was measured immediately after the end of infusion, on days 1 and 4 of therapy, and averaged to 72.29±11.6 and 74.02±19.29 μg/ml, respectively. Auditory function was evaluated in 10 children and no changes were observed before and after administration. Amikacin was found to be effective and safe in these children.

Amikacin 35 mg/kg was intravenously infused to 20 children, aged 1.8 to 22 years, with a mean age of 9.6±4.8 years, suffering from Pseudomonas aeruginosa pulmonary exacerbation and cystic fibrosis. Amikacin tolerance was determined for cochlear and renal functions [10]. The efficacy of this antibiotic was assessed by comparing nutritional, respiratory, inflammatory, and bacteriological parameters before and after 14 days of treatment. Total body clearance, distribution volume, AUC, and amikacin peak and trough concentrations were not different on days 1 and 14 of treatment. These authors concluded that amikacin was found to be effective and safe in these children.

Amikacin therapy in infants and children

Amikacin recommended doses in infants: Emergence of a multiply drug resistant Enterobacter cloacae, during a seven-week period in 1980, caused amikacin to become the aminoglycoside of choice in the initial management of suspected sepsis in a neonatal intensive care unit [11]. Recommended dose is 7.5 to 10 mg/kg loading dose, followed by a maintenance of 15 mg/kg, in two divided equal doses, and were administered intravenously to 5 infants with a body-weight ≤ 1,000 gram and 13 larger infants. Peak and trough concentrations exceeded 40 μg/ml and were 16.6±11.9 μg/ml, respectively.

System-specific parameters such as the clearance and distribution volume must be considered before amikacin administration to infants [12]. The development, of evidence-based dosing regimen using pharmacokinetic models is a major improvement, compared to empirical dosing regimen, and more emphasis should be put on the characterisation of amikacin pharmacodynamics in infants.

Amikacin initial dose was 10 mg/kg, followed by a maintenance dose of 7.5 to 10 mg/kg, was administered intramuscularly to 32 infants, with a body-weight < 2,000 gram, twice-daily, for 5 consecutive days [13]. With this dosing regimen, amikacin peak serum concentrations ranged

from 17 to 20 μg/ml and were consistent with amikacin therapeutic concentrations (15 to 25 μg/ml). Amikacin mean concentration ranged from 3.3 to 5.3 μg/ml. With this dosing regimen, serum concentration of 15 μg/ml inhibited Escherichia coli, Proteus, Enterobacter Klebsiella, Pseudomonas, Salmonella, Shigella and Staphylococcus aureus ranged from 91% to 100%. This proved useful therapy of eradicated gram-negative bacteria resistant to kanamycin. This dosing regimen yielded peak concentration within the therapeutic interval and it was found to be effective and safe in infants.

Amikacin pharmacokinetics were studied in 28 preterm infants, within the first week of life, with a mean body-weight of 1,380±471 gram [14]. This drug was intravenously infused at a dose of 7.5 mg/kg twice-daily, to infants, aged ≤ 7 days, and trice-daily to infants aged > 7 days. Elimination half-life, distribution volume, and total body clearance were 8.2±2.5 hours (range, 4.4 to 15.6), 0.57±0.11 L/kg (range, 0.39 to 0.84), and 0.84±0.28 L/h/kg (range, 0.48 to 1.45), respectively. This dosing regimen reduced the incidence of high trough levels and low peak levels in these preterm infants. *Amikacin once-daily dose in infants and children:* One-hundred-seventeen infants with a body-weight of 1,870±765 gram, received amikacin by intravenous infused according to the following dosing regimens: 20 mg/kg every 42 hours (postmenstrual age of < 28 weeks, group 1), 20 mg/kg every 36 hours (postmenstrual age between 31 and ≤ 34 weeks, group 2), 18.5 mg/kg every 30 hours (postmenstrual age between 34 and ≤ 37 weeks, group 3), 17.5 mg/kg every 24 hours (postmenstrual age ≥ 37 weeks, group 4), and 15,5 mg/kg every 24 hours, (postmenstrual age ≥ 37 weeks, group 5) [15]. Elimination half-lives (hours) were: 12.20±3.83, 8.40±1.36, 7.71±0.31, 6.77±0.32, and 5.55±0.49 in group 1, 2, 3, 4, and 5, respectively. Total body clearance (L/h/kg) were: 0.73±0.148, 0.82±127, 0.98±0.025, 1.09±0.061, and 1.15±0.038 in group 1, 2, 3, 4, and 5, respectively. These dosing regimens, based on the postmenstrual age, allowed achieving adequate first peak, and successive trough serum level, according to the recommended therapeutic concentration interval.

Fifty-six patients, including 9 infants, aged 5 to 9.5 months, and 47 children, aged 18 months to 14 years, were treated with amikacin (20 mg/kg) intravenously infused once-daily [16]. Twenty-five patients suffering from life-threatening infections, and seven patients suffering from chronic otitis median, were included in the study. Thirty-four cases received a β-lactam antibiotic, nine cases received other two antibiotics, five cases received metronidazole or vancomycin, in association with amikacin, and in 8 cases amikacin was a monotherapy. Amikacin serum concentration (μg/ml) was: 36±91 μg/ml 1 hour, 20.5±6.5 2 hours, 9.5±4.0, 4 hours, 2.7±2.2 8 hours, and 1.0±1.4 12 hours after administration. No toxicity was observed in any cases. This amikacin dosing regimen resulted to be affectivity, safety, and useful in this population.

Amikacin pharmacokinetics were studied in 35 children, aged 7.0±4.3 years, with a body-weight of 2.5±12.4 kg, suffering from severe gram-negative infections [17]. Dose of 15 mg/kg was administered once-daily, and trough concentration was 1.1±0.5 μg/ml on the 2nd day, and 1.4±1.6 μg/ml on the 5th day of treatment (N = 35). Peak concentration was 31.3±9.4 μg/ml on the 2nd day, and 32.4±7.4 on the 5th day of treatment (N = 35). This dosing regimen yielded trough and peak concentrations within the therapeutic interval. These results indicate that trough and peak concentrations can be predicted, with minimal bias, and reliable precision, in children. No nephrotoxicity and ototoxicity was observed. Amikacin once-daily dose of 15 mg/kg was found to be effective and safe in children.

Twenty-five children, with serious gram-negative infections, were treated with amikacin (20 mg/kg) intravenously infused, once-daily, for 4 to 12 consecutive days. In 9 cases, amikacin was co-administered with a β-lactam antibiotic [18]. Escherichia coli was the most frequent bacteria followed by Klebsiella pneumoniae, Providencia, and Enterobacter species heaving MICs ranging from 1 to 16 μg/ml. Peak and trough concentrations ranged from 49.0±13.5 to 53.6±13.4 μg/ml and 6.0±1.4 to 7.7±4.1 μg/ml, respectively. All children were clinically and bacteriologically cured, and no significant adverse-reactions were observed. This dosing regimen was found to be effective and safe in these children.

Amikacin administration once-daily versus twice-daily in infants and children

Kotze *et al.* [19] performed a placebo-controlled, randomized, prospective study to compeer potential toxic effects in term infants treated with amikacin once-daily or twice-daily. Impairment of renal glomerular function was defined as a decline < 50% of the expected physiological serum creatinine concentration. Brainstem auditory evoked potentials were also evaluated and amikacin serum concentration was measured. Fifteen infants, in once-daily group, and 12 infants in the twice-daily group, experienced at least one period of renal function impairment while were in hospital. In the once-daily dosing regimen, renal impairment and ototoxicity decreased to 5 of 16 and 4 of 16 infants, respectively, compared to the twice-daily dosing regimen, during follow-up. However, these differences were not statistically significant. Brainstem auditory evoked potentials did not find signs of ototoxicity at any time. Once-daily dosing regimen is not more toxic than the twice-daily dosing regimen, in infants.

Forsyth *et al.* [20] compared the efficacy and toxicity of once-daily versus twice-daily dosing regimen in children, aged 0.6 to 12 years, seriously ill, undergoing surgery. Children received either amikacin once-daily, at a dose of 15 mg/kg (N = 27), or 7.5 mg/kg twice-daily (N = 27). Cumulative dose, and duration of therapy, were significantly higher with the once-daily regimen. Efficacy (favourable, unfavourable or intermediate outcome) was assessed by child temperature, clinical improvement, and white cell counts. Serum creatinine concentration was measured after the end of therapy; pure tone air conduction audiometry, renal toxicity, and ototoxicity were also assessed. These parameters were not different in the once-daily and twice-daily dosing regimen. No unfavourable outcomes were observed, and no child developed nephrotoxicity or ototoxicity in these two dosing regimens, and mild high frequency hearing deficits were predominantly unilateral and reversible. Thus, both dosing regimens were found to be effective and safe in these children.

Twenty-three children suffering from different types of cancer, and receiving different chemotherapy for treating cancer, were enrolled [21]. All children had normal creatinine blood concentration. Children were allocated at random to receive amikacin (20 mg/kg), either once-daily or twice-daily. Serum samples were obtained after 72 hours to ensure that serum steady-state concentration was achieved. Peak and trough serum concentrations were measured 30 min after the start of infusion, and before the next infusion, respectively. Peak and trough concentrations, elimination half-life, total body clearance, and elimination rate constant were: 42.6±12.6, 0.18±0.24 μg/ml, 2.85±0.32 hours, 0.115±0.027 L/h/kg, and 0.242±0.02 h^{-1}, respectively, in the once-daily dosing regimen, and 19.1±12.3, 0.85±0.74 μg/ml, 2.51±0.74 hours, 0.266±0.168 L/kg/h, and 0.296±0.07 h^{-1}, respectively, in the twice-daily dosing regimen. These values were significantly different, with P-values of: <0.05, <0.05, < 0.05, 0.04, and 0.04, respectively. These authors recommended the use of once-daily dosing because peak concentration is higher, thus improves efficacy.

Twenty-one children, suffering from bronchopneumonia, aged 1.4±1.3 years, with a body-weight of 8.4±4.0 kg, and receiving ampicillin 100 mg/kg once-daily, were enrolled [22]. Amikacin was intravenously infused either once-daily (15 mg/kg), or twice-daily (7.5 mg/kg). Peak and trough concentrations were measured 30 min after the end of infusion and just before the next infusion, respectively, these values were: 39.4±9.6 and < 0.8 μg/ml, respectively, in the once-daily dosing regimen, and 20.0±9.6 and < 0.8 μg/ml, respectively, in the twice-daily. Peak concentration was significantly higher in the once-daily than in the twice-daily dosing regimen (P-value < 0.01). Total body clearance, and distribution volume were: 1.0±0.8 L/h/kg and 0.39±0.13 L/kg, respectively, in the once-daily dosing regimen, and 0.93±0.6 L/h/kg and 0.39±0.13 L/kg, respectively, in the twice-daily dosing regimen. Total body clearance and distribution volume were not different in the two dosing regimens. These authors recommended once-daily dosing regimen because yields higher peak concentration, and thus improves efficacy.

Outcomes of amikacin new dosing regimen in infants

A total of 181 infants, with a postmenstrual age of ≤ 27 to ≥ 37 weeks, and with a postnatal age of ≤ 7 to ≥ 8 days were enrolled [23]. Twenty-four infants were small for postmenstrual age, and 14 infants had intrauterine growth retardation. Amikacin doses were: 15 mg/kg in infants with a postnatal age of ≥ 8 days, and 12 mg/kg, in infants with a postnatal age ≤ 7 days. Dose intervals were 48 hours in infants with a postmenstrual age ≤ 27 weeks, 36 hours in infants with postmenstrual ages of 28 to 33 weeks, 24 hours in infants with a postmenstrual age ≥ 34 weeks, and 12 hours in infants with a postmenstrual age ≥ 37 weeks. Blood samples were collected around the time of the third dose to ensure that steady-state was achieved. Serum was separated from blood and used for amikacin concentration determination. Trough and peak concentrations were measured 30 min before the next dose, and 30 min after the end of the infusion, respectively. Infants in group 1 (empirical regimen, N = 107) received amikacin, once-daily and infants in group 2 were treated with amikacin once-daily (revised regimen, N = 74) based on pharmacokinetic results. Table 1 shows amikacin pharmacokinetic parameters in infants of groups 1 and 2. The distribution volume was significantly (P-value = 0.012) higher in infants of group 1 than in those of group 2.

Amikacin tissue concentrations infants and children

Tayman *et al.* [24] measured amikacin concentration in the epithelial lining fluid through branch alveolar lavage in infants with postmenstrual and postnatal ages of 31.9 weeks (range, 24.1 to 37.2) and 3.5 days (range, 2.5 to 3.7), respectively. Amikacin was administered intravenously once-daily, and the median peak and trough serum concentrations (μg/ml) were: 39.1 (range, 24.1 to 43.2), and 2.1 μg/ml (range, 2.0 to 3.7), respectively. Peak and trough concentrations (μg/ml) were 41.0 (range, 24.1 to 46.0) and 6.5 (range, 2.0 to 25.0), respectively, in the epithelial lining fluid, and peak concentration was reached between 6.0 and 14.6 hours.

Table 1. Amikacin pharmacokinetic parameters in 107 infants of groups 1 (empirical regimen) and in 74 infants of group 2 (revised regimen). Figures are the mean±SD, by An SH [23]

Variable	Group 1 (N=107)	Group 2 (N=74)	*P-value
Distribution volume (L/kg)	0.56±0.13	0.52±0.09	0.012
Elimination half-life (hours)	6.0±4.1	5.90±3.70	0.236
Elimination rate constant (hour^{-1})	0.137±0.063	0.151±0.066	0.118
Total body clearance (L/h/kg)	0.074±0.035	0.075±0.030	0.886

*Unpaired t test.

Amikacin concentration was measured in bronchial effusion of 18 children with bronchopulmonary infection and cystic fibrosis [25]. Amikacin was intravenously infused at a daily dose of 35 mg/kg for 14 consecutive days, and was co-administered with ceftazidime or imipenem. Peak and trough serum concentrations (μg/ml) were 121.4±37.5 (range, 42.7 to 176), and 0.88±0.62 (range, 0.2 to 1.9), respectively. In sputum, peak concentration was 10.9±7.5 μg/ml (range, 5.1 to 19), and remained above 8 μg/ml for at least 4 hours after infusion.

Amikacin concentration was measured in bronchial effusion of 36 children, aged 7.6 years (range, 3 to 15), suffering from bronchopulmonary infection caused by Pseudomonas aeruginosa (N = 14) and Staphylococcus aureus (N = 2), and thirty-two children had cystic fibrosis [26]. Amikacin was intravenously infused at doses of 5 mg/kg every 6 hours (N = 17), and trice-daily (N = 10), 7.5 mg/kg every 6 hours (N = 4), twice-daily (N = 2), and to 12.5 mg/kg twice-daily (N = 3). Amikacin was co-administered with fosfomycin, or ceftazidime, or piperacillin, or ticarcillin whereas, in non-cystic fibrosis and with azlocillin, or fosfomycin, in cystic with fibrosis children. Peak serum concentrations (μg/ml) varied according to the administered dose, and ranged from 9.0 to 43.8. In sputum, concentrations (μg/ml) were 1.38±0.97 after a dose of 5, 1.0±1.6 after a dose of 7.5, and 2.35±0.07, after a dose of 12.5 mg/kg, 1 hour after administration. The sputum to plasma peak ratio ranged from 0.11 and 0.16. In bronchial effusion, the concentration was lower MICs of Pseudomonas aeruginosa and Staphylococcus aureus, thus could not eradicate these infective agents.

Amikacin concentrations were measured in serum, muscle, and in fat tissue of 41 children treated with 7.5 mg/kg amikacin intramuscularly twice-daily [27]. Mean amikacin peak concentration (μg/ml) was 14.9 in serum, 2.2 and in muscle, and 1.89 in fat tissue; then the concentration declined rapidly in these tissues. The concentration exceeded 1 μg/g in muscle for at least 3 hours and in fat tissue for at least 4 hours.

Amikacin penetration into the cerebrospinal fluid of infants and children

Allegaert *et al.* [28] measured amikacin concentration in the cerebrospinal fluid of 44 infants, in the first week of life, who had a mean postmenstrual age of 36 weeks (range, 26 to 41), and a mean body-weight of 2,430 gram (range, 870 to 3,860). Amikacin (15 mg/kg) was administered by lumbar puncture, and peak serum concentration was 35.7±5.9 μg/ml. The median time interval between amikacin administration and the cerebrospinal fluid initiation was 25 hours (range, 2.5 to 93.7). Peak cerebrospinal fluid concentration was 1.08 μg/ml (range, 0.34 to 2.65) and correlated with serum concentration (P-value < 0.01). The median equilibration half-life between serum and cerebrospinal fluid was 7.5 hours. Cerebrospinal fluid concentration had a remarkable interindividual variability, the coefficient of variation was 49.1%, and the partition coefficient was 0.103.

Amikacin penetration into the cerebrospinal fluid was studied in 16 children, aged 4 months to 8 years, with bacterial meningitis [29]. Amikacin was intravenously infused at a dose of 7.5 mg/kg twice-daily. Cerebrospinal fluid was sampled on day 1 of therapy, which is at the expected time to achieve peak concentration in this fluid. Amikacin penetrated the blood-barrier substantially and achieved a concentration of 1.65±1.6 μg/ml.

Amikacin penetration into the cerebrospinal fluid was investigated in 20 children suffering from acute bacterial meningitis [30]. Amikacin (7.5 mg/kg) was administered intramuscularly twice-daily, and was co-

administered with ampicillin 75 mg/kg, every 6 hours, intravenously, in 6 children. The concentration in the cerebrospinal fluid followed the same pattern of that in serum, and serum to cerebrospinal fluid concentration ratio was 3:1, at 7 hours after dosing. All children underwent clinical improvement. A minimum cerebrospinal fluid concentration of 2 μg/ml was found in 76% of children, 0.5 to 7 hours after administration. Child response was predictable by a correlation of in-vitro MIC values with in-vivo amikacin cerebrospinal fluid concentration.

Amikacin intraventricular concentration in children

Ten hydrocephalic children, aged 1 month to 6 years, with suspected ventricle-peritoneal shunt infections were enrolled. Five children were affected by gram-negative bacilli. Amikacin was intravenously infused at dose of 7.5 mg/kg every 8 hours [31]. Blood samples were collected for 7 times (ranging from 30 min to 7 hours), and ventricular fluid samples were obtained 7 hours after dosing to assure that the ventricular fluid samples were from the ventricular system and not from the extra-ventricular drainage catheter. Blood and ventricular fluid were sampled after the forth or fifth amikacin dose. Peak serum concentration ranged from 16.5 to 29.0 μg/ml, with elimination half-life of 2.2±1.1 hours (range, 1.1 to 4.6). Ventricular fluid and serum concentrations were: 3.4±3.6 μg/ml and 24.1±3.1 μg/ml, respectively, and the serum to ventricular fluid ratio was 14.1±13.5%. Concentrations were: 6.3±1.8 and 0.4±0.21 μg/ml (P-value < 0.0001), in 5 children affected by gram-negative bacilli, and in the remaining 5 children without infection, respectively. The serum to ventricular fluid ratios were: 26.4±5.7 and 1.8±0.6 (P-value < 0.0001), respectively, in these children. Maintenance of high concentration in the ventricular fluid reduced the presence of the infecting organisms up at least 10 days. The MIC of infecting gram-negative bacilli was ≤ 1 μg/ml, thus the concentration in the ventricular fluid is several times higher than the MIC of the infective agents, suggesting that the scheduled dosing regimen is appropriate eradicate the infecting gram-negative organisms in the intraventricular fluid.

Amikacin pharmacokinetics in infants and children

Amikacin pharmacokinetics were studied in 37 infants, aged 1.13±8.7 days (range, 1 to 34), with a birth-weight of 2,440±756 gram [32]. Amikacin was administered, either intramuscularly or intravenously, at a dose of 7.5 mg/kg once-daily. Peak concentration was reached 32 min after intramuscular administration, suggesting that amikacin is rapidly absorbed from the muscular depot. Elimination half-life, elimination constant rate, distribution volume, and the total body clearance were: 357±122 min, 0.0021±0.0007 min^{-1}, 0.66±0.19 L/kg, and 1.42±0.57 L/h/kg, respectively. Serum concentration achieved the steady-state 8 min after administration, the mean concentration was 10 μg/ml, and this concentration was maintained for 6 to 8 hours. Serum concentrations obtained with different doses, and at various administration times, are reported in table 2. This table shows that concentrations were not different according to different administration times, but were different according to doses. Doses were administered trice-daily, and were calculated on the basis of postnatal age. At postnatal ages of 1, 5, 10, 15, 20, 25, and 30 days, dosing regimens consisted of a loading dose of 15 mg/kg, followed by maintenance doses of: 4, 5, 6, 7, 8, 9, and 10 mg/kg, once-daily, respectively.

Amikacin population pharmacokinetics were studied in infants by Wang *et al.* [33] and Botha *et al.* [34]. Wang *et al.* [33] enrolled 94 infants with median postmenstrual, postnatal ages, and body-weight of 38±4 weeks, 10±7 days, and 2,910±960 gram, respectively. Amikacin population analysis was performed using the Monte Carlo analysis, and the resulting serum elimination half-life, elimination rate constant, total bogy clearance, and distribution volume were: 219±3.3 min, 11.4±4.8 min^{-1}, 103±25 L/h/kg, and 0.55±0.16 L/kg, respectively. The interindividual variability of these parameters were: 45.2%, 42.1%, 24.3%, and 29.1%, respectively. Peak and trough serum concentrations (μg/ml) were: 20 to 25 and < 5 μg/ml, respectively. The percentage of infants, that exceeded serum concentration of 1 μg/ml, at 0.5, 4, 8, and 12 hours were 14.6, 22.9, 37.5, and 45.8, respectively. These parameters, obtained with a population pharmacokinetics, are similar with those reported by Sardemann *et al.* [32], and both studies revealed a remarkable interindividual variability of pharmacokinetics parameters. Such a relevant variability requires an important attention to treat infants with amikacin, whose dose should be calculated according to the postnatal age.

Fifty-three black infants with postmenstrual, postnatal ages, and body-weight of: 35.1±3.6 weeks, 6.3±3.3 days, and 2,105±807 grams, respectively, were enrolled [34]. Amikacin was administered either with a loading dose of 17.5 mg/kg, followed by a maintenance dose of 15 mg/kg once-daily, or a loading dose of 10 mg/kg, followed by a maintenance dose of 7.5 mg/kg twice-daily. Doses were administered by intravenous bolus. One- and two-compartment models were compared using the corresponding subroutines from the NONMEN library. Date, that are reported hereafter, are expressed as the mean and (95% confidence interval). Clearance, elimination half-life, and distribution volume were: 2.88 L/h/kg (range, 2.70 to 3.00), 381 min (range, 369 to 394), and 0.434 L/kg (range, 0.414 to 0.453), respectively. Pharmacokinetic parameters were not influenced by the gender, postmenstrual and postnatal ages. Amikacin is filtered almost unchanged by the glomerular filtration, thus clearance is depending by the glomerular filtration rate, and varies with the infant maturation.

Nine cystic fibrosis children, aged 7.6 years (range, 3 to 15), with a body-weight of 20 kg (range, 15 to 29), and suffering from Pseudomonas aeruginosa infection, were recruited [35]. Amikacin was intravenously infused at the following doses: of 5, 7.5, and 10 mg/kg once-daily, and 12.5 mg/kg twice-daily. The time intervals between two consecutive doses were: 6 to 12 hours, according to the bacterial sensitivity, and amikacin was co-administered with azlocillin, or piperacillin, or ceftazidime, or fosfomycin, or ticarcillin. Blood samples were collected, prior treatment, and at 0.5, 1, 2, and 4 hours after infusion. Sputum samples were obtained 1, 2, and 4 hours after

Table 2. Amikacin serum concentration (μg/ml) obtained with different doses, and at different times after administration. Amikacin was administered, intravenously or intramuscularly, to 37 infants aged 1 to 34 days. Figures are the mean±SD, by Sardemann *et al*. [32]

Time after dosing (min)	Amikacin conc. (μg/ml)	Amikacin dose (mg/kg)	Amikacin conc. (μg/ml)	Amikacin dose (mg/kg)	Amikacin conc. (μg/ml)	*P-value
30±10	15.6±2.5	7.2	15.4±3.8	7.2	27.7±1.1	> 0.05
30±10	13.0±4.8	4.0	19.2±5.7	7.2	22.9±8.9	< 0.001
30±10	12.1±2.7	4.0	17.5±5.1	5.0	21.7±9.5	< 0.001
*P-value	0.4016	---	0.5256	---	0.5178	---

Conc.=concentration. *One-way analysis of variance.

the end of infusion. Serum elimination half-life, elimination rate constant, clearance, and distribution volume were 0.94±0.25 hours, 0.74±0.25 hours^{-1}, 130±32 ml/min/1.73m^2, and 0.26±0.06 L/kg, respectively. Peak serum concentration was 19±3.4 to 31.7±5.3 μg/ml, high concentration was maintained for at least 2.7 hours, and exceeded the MIC of Pseudomonas aeruginosa (4 μg/ml). Concentration was 1.0 to 3.6 μg/ml in sputum, thus was lower than the MIC of Pseudomonas aeruginosa. Likely, the concentration in bronchial effusion could not eradicate this infective agent.

Cleary *et al.* [36] measured amikacin serum concentration in 50 children aged 11 months to 16 years. Children were stratified accordingly to their age (years): 1 to 6 (group 1), 7 to 11 (group 2), and 12 to 16 years (group 3). Serum concentration (μg/ml) was: 13.6±1.5, 9.5±1.1, 5.7±0.7, 1.5±0.4, 0.4±0.1, and 0.4±0.1 respectively, in group 1, 18.1±3.2, 11.4±2.0, 9.0±1.7, 4.2±1.0, 1.6±0.5, and 0.7±0.3, respectively, in group 2, and 17.2±1.7, 11.4±1.2, 8.3±0.1, 3.3±0.7, and 1.2±0.3, respectively, in group 3. Amikacin serum concentration was not measured at 8 hours in group 3. Amikacin serum concentration was significantly different in these 3 groups, and the P-values were <0.0001 to 0.0001, tested by one-way analysis of variance. Serum concentration varied according to the children age, and the lowest values were found in the youngest children (group 1).

Ten children affected by kwashiorkor, aged 1.68±0.98 years (range, 1 to 4), with a body-weight of 8.3 kg (range, 5 to 15) were included in the study [37]. Blood samples (1 ml) were collected prior, and 0.5 and 6 hours, after administration. Peak and trough plasma concentrations (μg/ml) measured at 0.5 and 6 hours after administration, were: 16.60±4.90 and 3.85±2.69, respectively. Half-life, elimination rate constant, clearance, and distribution volume were: 2.53 hours, 0.30±0.09 hour^{-1}, 0.10±0.04 L/h/kg, and 0.33±0.09 L/kg, respectively. Peak concentrations are similar to those obtained in the studies above reported [32-36].

Catherine *et al.* [38] studied amikacin population pharmacokinetics in 73 burn children, aged 4.5 years (range, 0.6 to 17), and with a body-height of 20 kg (range, 8 to 90). Thirty-seven children were white, 15 were black, 16 were Hispanic, 3 were Asian, and 2 were Pacific Islander. Dose was 16.4±3.9 mg/kg (range, 4.9 to 22.3), and sixty-two children (84.9%) were treated with vancomycin. Two-compartment model, with firs-order elimination, fitted disposition better than the one-compartment. Using univariate analysis, bogy-weight and concomitant administration of vancomycin, were identified as having significant influence upon pharmacokinetics, with respective P-values of < 0.01, and < 0.05. The pharmacokinetic parameters hereafter reported are expressed as the mean and (95% confidence interval). Clearance, distribution volume of the central compartment, inter-compartmental clearance, and distribution volume of the peripheral compartment were scaled to an individual of 70 kg, and resulted to be: 5.98 L/h/70 kg (range, 4.97 to 6.99), 16.7 L/70 kg (range, 14.0 to 19.4), 3.8 L/h/70 kg (range, 2.44 to 4.32), and 40.1 L/70 kg (range, 15.8 to 80.4), respectively. Interindividual variability was 8.7% (range, 4.2 to 13.3), 6.0% (range, 4.4 to 12.1), 0.01, and 0.02, respectively, thus, there was a remarkable interindividual variability.

Impact of development on amikacin pharmacokinetics

Nephrogenesis in humans starts at approximately day 30 of postmenstrual age and ends before the 36th week of gestation. By a complex interaction between the metanephric mesenchyme and the ureteric bud, nephrons are formed to a total of 600,000 to 800,000 per kidney, with a wide interindividual variability. Intrauterine growth restriction has been shown to lead to a low nephron number in humans. Premature birth has also been shown to lead to fewer nephrons [39]. Amikacin recommended dose is 12 mg/kg every 36 hours in infants in the first week of life. One-hundred-sixty-one infants, with a postmenstrual age and birth-weight of 32.4±3.9 weeks, and 1,650±651 gram, respectively, were included in the study. One blood sample was collected before the first, and after the second dose. Pharmacokinetics were adequately fitted by one-compartment model. Clearance inversely correlated with birth-weight and postmenstrual age. These findings reveal that both intrauterine growth restriction and prematurity impair glomerulus filtration rate on the first days of life. Glomerulus filtration rate increases with infant maturation, and amikacin clearance was significantly lower in infants with lower birth-weight, and higher in infants with higher postmenstrual age. Clearance and distribution volumes were: 0.58 L/h/kg (range, 0.50 to 0.73) and 0.52 L/kg (range, 0.51 to 0.53). Clearance correlated with both birth-weight and postmenstrual and the respective P-value was < 0.01 for these two parameters.

The effect of intrauterine maturation on amikacin disposition was studied in 29 infants affected by gram-negative bacteria infection. The postmenstrual, postnatal ages, and the birth-weight were 34.5±3.3 weeks (range, 28 to 42), 1 to 2 days, and 1,980±920 gram (range, 920 to 4,500), respectively [40]. A percentage of 34, 59, and 70 infants were small, large, and normal for postmenstrual age, respectively. Amikacin was intravenously infused at a dose of 7.5 mg/kg twice-daily, pharmacokinetics were better fitted by a two-compartment model, a remarkable interindividual variability was observed in pharmacokinetic parameters, and infants, with a postmenstrual aged < 34 weeks, had a higher drug accumulation. Elimination half-life, clearance, and distribution volume were inversely correlated with infant maturation and with intrauterine maturation. Elimination half-life, clearance, and distribution volume were: 62.85±33.24 hours, 0.86±0.29 L/h/kg, and 0.80±0.23 L/kg, respectively. Half-life was longer in preterm than in term infants previously reported [32-34].

Amponsah *et al.* [41] performed a prospective, nonrandomized, single-site study to establish the relationship between postnatal age and amikacin pharmacokinetics. Two-hundred-seven infants with postmenstrual, postnatal ages, and birth-day of 35 weeks (range, 25 to 44), 1.23 days (range, 0.16 to 21.75), and 2,300 gram (range, 900 to 5,200), respectively, were enrolled. Amikacin was intravenously infused, the loading dose was 15 mg/kg, and was followed by a maintenance dose of 7.5 mg/kg twice-daily. Cloxacillin was co-administered with amikacin to treat gram-negative bacteria infection. Aminophylline was also co-administered with amikacin. Peak concentration was not different between term and preterm infants, whereas trough concentration (μg/ml) was higher in preterm (9.5±5.7) than term infants (9.2±5.7) (P-value = 0.02). Birth-weight is the most important determinant for clearance, and glomerular filtration rate increases with infant maturation, and amikacin is mostly cleared renally. Table 3 shows optimal peak and through concentrations in term and preterm infants. Optimal amikacin peak and trough concentrations are < 20 and < 5 μg/ml, respectively.

Lanao *et al.* [42] measured amikacin pharmacokinetic parameters during infant development to establish the relationship between infant maturation and amikacin pharmacokinetics. Six infants, aged 11.5±6.5 days (range, 6 to 25), 10 young children aged, 9.5±4.7 months (range, 4 to 18), and 8 children, aged 5.9±2.6 years (range, 3.1 to 11.3), were enrolled. Amikacin single intravenous dose of 7.5 mg/kg was administered to all patients. Serum concentration ranged in a wide

Table 3. Amikacin peak and trough concentrations (μg/ml) obtained in 21 term and 25 preterm infants. Amikacin was intravenously infused (loading dose=15 mg/kg; maintenance dose=7.5 mg/kg twice-daily). Figures are the proportion of infants with amikacin peak and trough concentrations below, within, and above the optimal amikacin regimen, by Amponsah *et al*. [41]

	Peak (N=21)			**Trough (N=25)**		
Infant	> 35 μg/ml	20 - 35 μg/ml	< 20 μg/ml	< 5 μg/ml	5 - 10 μg/ml	> 35 μg/ml
Term	3/21 (14.3%)	7/21 (33.3%)	11/21 (52.4%)	5/25 (20.0%)	16/25	4/25 (16%)
	Peak (N=28)			Trough (N=36)		
Preterm	6/28 (21.4%)	10/28 (35.7%)	10/28 (35.7%)		22/36 (61.1%)	9/36 (25.0%))
*Comparison of proportions	0.2	0.7	0.7	0.3	0.7	0.1

*P-value based on x^2 test.

interval, in the tree groups of infants. Half-life decreased with patient age, whereas clearance and distribution volume were not different in the three groups studied. Elimination half-lie, clearance, and distribution volume were: 1.80±0.65 hours, 2.99±1.05 L/h/kg, and 2.99±1.05 L/kg, respectively, in infants and young children, and these values were 1.20±0.12 hours, 2.83±1.365 L/h/kg, and 4.11±3.114 L/kg, respectively, in children. Elimination half-life was significantly (P-value = 0.0223) longer in infants and young children than in children.

Tréluyer *et al.* [43] described amikacin pharmacokinetics in 49 infants, 77 older infants, and 29 children with a mean, median and range of postmenstrual, postnatal ages, and body-weight of: 38, 39 (range, 30 to 41) weeks, 450, 691 (range, 1 to 3,650) days, and 7,380, 4,832 (range, 1,350 to 3,352) gram, respectively, for these 155 subjects. Amikacin was intravenously infused at a median dose of 7.44 mg/kg (range, 2.47 to 14.9). Pharmacokinetics were better fitted by one-compartment model. Pharmacokinetic parameters hereafter reported are expressed as the mean, median, and range. In these 155 subjects, half-life, clearance, and distribution volume were: 2,77, 2.04 (range, 0.52 to 21.76) hours, 0.123, 0.116 (range, 0.0995 to 0.250) L/h/kg, and 0.337, 0.312 (range, 0.138 to 0.846) L/kg, respectively. The interindividual variability was 98%, 52%, and 39%, respectively. High variability of clearance and distribution volume was accounted by postnatal age and body-weight. Clearance and distribution volume correlated with postnatal age. Creatinine plasma concentration accounted for large interindividual variability of clearance, but a less pronounced effect was observed for the body-weight. Pattern of clearance changing, normalized for body-weight, was a function of postnatal age, and an extreme variability was observed in the first weeks of life. Clearance increased very rapidly during the first month of life, but continued to increase, much less rapidly, thereafter. Distribution volume decreased rapidly during the first weeks of life, and continued to decrease thereafter.

Impact of diseases on amikacin pharmacokinetics in children

Liu *et al.* [44] studied the effect of burn and cancer on amikacin pharmacokinetics in children. Sixty-six burn children and 112 children with cancer were recruited. Both demographic and pharmacokinetic parameters hereafter reported are expressed as the median and (5^{th} and 95^{th} percentiles). The age and weight were 5.0 years (1.0 to 15.0) and 20.5 kg (10.1 to 79.0), respectively, in children with burn injuries, and 6.3 years (0.9 to 17.5), and 20.6 kg (8.8 to 62.2), respectively, in children with oncologic diagnosis. Amikacin dose and serum concentrations were obtained by drug monitoring in hospitalized children, either with burn and malignancy. Pharmacokinetics were better fitted by a two-compartment model with first-order elimination (Table 4). Stepwise covariate search demonstrated significant improvement of model fitting by incorporating disease condition, weight, age, and creatinine clearance. Covariates obtained with the optimal dosing regimen are included in table 4. Burn patients had 55% (95% confidence interval = 1% to 28%) higher clearance and 17% (95% confidence interval = 1% to 34%) higher distribution volume than patients with cancer.

Lanao *et al.* [45] studied 18 hospitalized children, of whom, 8 had normal renal function, and the remaining 10 children had varying degrees of renal impairment. Children with normal renal function were aged 5.9±2.6 years, had a body-weight, serum creatinine concentration, and creatinine clearance of 19.4±4.0 kg, 0.53±0.07 mg/dl, and 99.7±25.0 ml/min x 1.73m^2, respectively. Children with renal impairment were aged 6.6±3.9 years, and had the above reported parameters of: 19.3±9.7 kg, 1.51±2.01 mg/dl, 45.80±22.1 ml/min x 1.73m^2, respectively. Higher serum creatinine concentration and lower creatinine clearance were observed in children with renal impairment than in children with normal renal function (P-value < 0.0001, for both parameters). An amikacin intravenous single dose of 7.5 mg/kg was administered to all children and pharmacokinetic parameters are reported in table 5. This table shows that all pharmacokinetic parameters are altered in children with renal impairment. Elimination from the body, as expressed as the half-life and the clearance, is lower in sick children, thus the dose should be reduced in children with renal impairment.

Amikacin interindividual variability of pharmacokinetics in infants

Thirty-one infants, with postmenstrual, postnatal ages, and body-weight of 37 to 42 weeks, 0 to 7 days, and 3,370 to 3,440 gram, respectively, were enrolled (Vučićević *et al.* [46]). All children had normal renal and liver functions, and these authors assessed peak and trough interindividual variability. Amikacin was intravenously infused at doses of 15 mg/kg once-daily, or 7.5 mg/kg twice-daily, and was co-administered with β-lactam antibiotics, to treat infections caused by Acinetobacter species, and Escherichia coli (2 infants) and Staphylococcus aureus and Pseudomonas aeruginosa (3 infants). Two blood samples were collected after the end of infusion and before the next dosing, respectively. Peak and trough serum concentrations varied remarkably. Peak concentration (μg/ml) was < 15 in two infants (12.5%), and > 30 in the raining 29 infants in the twice-daily group. Trough concentration (μg/ml) was > 10 in 2 infants (12.5%) and < 5 in the raining 29 infants. Further analysis revealed that neonatal age contributes to change peak and trough concentrations. Half-life was longer and clearance were lower in infants aged ≤ 2 days than in infants aged > 2 days whereas, the distribution volume was similar in two groups of infants. Such variability was due to the renal maturation, as amikacin is mainly eliminated renally.

Bleyzac *et al.* [47] studied amikacin population pharmacokinetics in 131 infants with median postmenstrual, postnatal ages, and birth-weight of 24 weeks (range, 24 to 41), 2 days, and 670 to 3,570 gram, respectively. Amikacin (15 mg/kg) was intravenously infused once-daily. Two blood samples (0.5 ml) were drawn 30 min and 18 hours after administration. Mean and median elimination rate constant were: 0.0420 and 0.0491 $hour^{-1}$, respectively, in infants with a postmenstrual age of 24 weeks, and 0.1198 and 0.1214 $hour^{-1}$, respectively, in infants with a postmenstrual age 41 weeks. Mean and median clearance were:

Table 4. Amikacin pharmacokinetic parameters in 66 burn children, aged 5.0 years, and 112 children with cancer, aged 6.3 years. Figures are the median (percentage relative standard error), 95% confidence interval, and the mean. Base parameter includes both burn children and children with cancer, by Liu *et al*. [44]

Parameters	Base	Optimal		Bootstrap	
	Median (RSE%)	Median	95% CI	Mean	95% CI
Clearance (L/h)	2.73 (6.4)	2.12	1.79 - 2.46	2.10	1.76 - 2.48
Central distribution volume (L)	1.66 (14.6%)	5.70	4.64 - 6.76	5.71	4.47 - 6.73
Distribution clearance (L/h)	1.29 (10.0%)	0.71	2.36 - 7.22	4.97	3.09 - 8.84
Peripheral distribution volume (L)	8.53 (10.5%)	4.79	2.36 - 7.22	4.79	3.09 - 8.84
Children with cancer	---	0	---	0	---
Burn children	---	0.55	0.28 – 0.82	0.58	0.29 – 0.87
Central volume distribution (L)					
Children with cancer	0	---	0	---	
Burn children	---	0.55	0.28 – 0.82	0.58	0.29 – 0.87
Between subject variability	Median (RSE%)	Median	RSE%	Mean	RSE%
Variance of residual variability for CL	0.18 (14.9%)	0.06	20.0%	0.06	44.5%
Variance of residual variability for CVD	---	0.04	41,5%	0.04	44.5%
Variance of residual variability for DC	0.08 (54.3%)	---	---	---	---
Residual error	Median (RSE%)	Median	RSE%	Mean	RSE%
Variance of residual (proportional)	0.10 (12.2%)	0.06	15.8%	0.06	15.8%

RSE%=percentage relative standard error. CVD=Central volume distribution. DC=distribution clearance. 95% CI=95% confidence interval.

Table 5. Amikacin pharmacokinetic parameters obtained in 8 children, aged 5.9±2.6 years, with normal renal function, and 10 children, aged 6.6±3.9 years, with renal impairment. Amikacin single intravenous dose was 7.5 mg/kg. Figures are the mean±SD, by Lanao *et al*. [45]

Pharmacokinetic parameter	Children with normal renal function	Children with renal impairment	*P-value
Rapid disposition half-life (hour)	0.251±0.117	1.108±0.400	0.0009
Slow disposition half-life (hour)	1.930±0.194	6.357±0.233	0.0001
Elimination rate constant of the rapid disposition phase ($hour^{-1}$)	1.034±0.615	0.310±0.026	0.0021
Elimination rate constant of the slow disposition phase ($hour^{-1}$)	1.217±0.301	0.347±0.233	0.0002
Overall elimination rate constant ($hour^{-1}$)	1.631±0.637	0.344±0.160	0.0002
Total body clearance (L/h/kg)	3.008±1.247	1.500±0.624	0.0040
Central distribution volume (L)	2.272±1.384	4.112±1.827	0.0024
Peripheral distribution volume (L)	1.767±1.909	2.729±1.636	0.0002
Distribution volume at steady-state (L/k)	0.198±0.107	0.370±0.188	0.0012

*Unpaired t test.

0.0061 and 0.0063 L/h, respectively, in infants with a postmenstrual age of 24 weeks, and 0.1349 and 0.1349 L/h, respectively, in infants with a postmenstrual age of 41 weeks. Elimination rate constant correlated with postmenstrual age. Mean and median distribution volume were: 0.2006 and 0.2026 L/kg, respectively, in infants with a postmenstrual age 24 weeks, and 0.3229 and 0.3427 L/kg, respectively, in infants with a postmenstrual age of 41 weeks. The observed reduction in elimination rate constant and clearance is due to renal maturation, and the increase in distribution volume is related to an increase in lean body mass.

Allegaert *et al.* [48] identified and quantify factors describing amikacin variability of clearance in preterm infants. Population pharmacokinetics were estimated in a cohort of 205 extreme premature infants with a postmenstrual age of 27.8±1.8 weeks (range, 24 to 30). Covariate analysis included birth-weight, postmenstrual age, Apgar score, prophylactic administration of a nonsteroidal anti-inflammatory drug to the infant, maternal indomethacin and betamethasone administration, and chorioamnionits. A one-compartment linear disposition model with zero order input (0.3 hour infusion) and first-order elimination was used. Distribution volume was 40.2 L/kg, and clearance increased from 0.486 L/h/70 kg to 0.940 L/h/70 kg by 30 weeks of postmenstrual age. Interindividual variability for clearance and distribution volume were 0.336 and 0.451, respectively. The use of an anti-inflammatory drug, in the first day of life, reduced amikacin clearance by 22%. Overall 65% of clearance variability was predictable. Birth-weight explained 48%, postmenstrual age 15%, and anti-inflammatory drug 2% of variability. Size and postmenstrual age are the major contributors to clearance variability in extreme premature infants with a postmenstrual age < 31 weeks. The large (35% of total) unexplained variability of clearance reinforces the need for target concentration intervention to reduce variability in exposure to safe and effective range.

Amikacin optimisation dosing regimen in infants and children

Kenyon *et al.* [49] proposed a new amikacin dosing regimen to improve amikacin efficacy and safety in preterm infants. Fifty-eight infants with a postmenstrual age and birth-weight of 30.6±3.5 weeks and 1,310±506 gram received an amikacin dose of 7.5 mg/kg trice-daily, in infants aged > 7 days, and 7.5 mg/kg twice-daily, in infants aged < 7 days (old regimen). This dosing regimen yielded > 50% of unacceptable trough concentration > 10 μg/ml and peak concentration < 20 μg/ml in 37% of infants. The proposed (optimal) dosing regimen consisted of an amikacin dose of 7.5 mg/kg, and intervals between doses were 15 and 12 hours for infant aged < 7 days, and > 7 days, respectively. Twenty-nine infants, with a postmenstrual age and birth-weight of 31.45±5.32 weeks and 1,730±1,015, gram, respectively, were included in the study (new dosing regimen). Thus, the two groups of infants had the same demographic data. With the old dosing regimen, peak concentration was > 30 μg/ml in 67%, and was < 20 μg/ml in 85% of infants. Trough concentration was ≤ 10 μg/ml in 68,42% of infants and > 10 μg/ml in 2.75%, and the relative doses were 20 to 30 mg/kg. With

the new (optimal) dosing regimen, amikacin peak concentration was > 30 μg/ml in 72,41% of infants and < 20 μg/ml in 3,57% of infants, and trough concentration was ≤ 10 μg/ml in 55,17% of infants and < 10 μg/ml in 78,57% of infants, and the relative dose was 20 to 30 mg/kg. The new amikacin dosing regimen yielded higher amikacin peak and lower through concentrations, and thus the new dosing regimen is preferable.

Alqahtani *et al.* [50] determined amikacin population pharmacokinetic parameters in paediatric patients, in order to estimate optimal dosing regimen. Sixty-seven children, aged 4.9±3.9 years, with a body-weight of 15.2±8.4 kg, were enrolled. Amikacin was intravenously infused at a dose of 23.0±7.3 mg/kg once-daily. Peak and trough concentrations (μg/ml) were 20.7±7.6, and 2.4±1.7, respectively (conventional dosing regimen). The optimal dosing regimen consisted of 30 to 40 mg/kg amikacin intravenously infused once-daily. The conventional regimen yielded only 42% of peak concentration within target value of 20 to 40 μg/ml. These authors performed target attainment rates analysis for various dosing regimens at different MIC values to estimate the probability of achieving an amikacin peak concentration to MIC ratio ≥ 8. The conventional dosing regimen (20 to 30 mg/kg once-daily) yielded pharmacokinetics/pharmacodynamics target peak concentration in 90% of children for an MIC ≤ 2 μg/ml, whereas the probability of achieving an Cmax/MIC ratio ≥ 8 was < 20% for an MIC > 4 μg/ml. In the optimal dosing regimen, the probability of achieving an MIC ratio ≥ 8 is > 40%. Table 6 shows that the interindividual variability of clearance and distribution volume is lower with optimal than with the conventional dosing regimen, and the clearance and distribution volume are higher with the optimal than with conventional dosing regimen.

Yu *et al.* [51] developed amikacin optimal dosing regimen for treatment of gram-negative bacteria sepsis in children with and without burn. Seventy burn children, aged 4.5 years (range, 2.0 to 10.0), and weighing 20.0 kg (range, 13.0 to 49.0), and 32 children without burn injuries aged 7.0 year (range, 2.0 to 14.0), and weighing 22.9 kg (range, 14.8 to 46.3) were recruited. The conventional dosing regimen consisted of a median dose of 15 mg/kg amikacin, administered twice-daily, and peak and trough concentrations (μl/ml) were 19.1 (range 17.4 to 28.2), and 0.9 (range, 0.5 to 1.8), respectively. The new (optimal) dosing regimen was selected in order to generate the greatest minimization of the objective function value, to reduce interindividual variability, and to decrease residual unexplained variability. Optimal dosing regimen was evaluated in terms of achieving pharmacodynamic target rates (Cmax/MIC ≥ 8) with susceptible isolate MIC values ranging from 0.5 to 8 μg/ml. To improve pharmacokinetic target attainment rates, larger doses (≥ 25 mg/kg) were used at dosing intervals of 6 to 24 hours, with MIC values spanning 0.5 to 8 mg/kg. Optimal dosing regimen achieved a Cmax/MIC ≥ 8 in 90% of children. Median amikacin dose of 16 mg/kg every 8 hours, peak and trough concentrations were 32.0 μg/ml (26.4 to 37.5), and 2.3 μg/ml (1.5 to 3.5), respectively new. Table 7 shows that the interindividual variability, for clearance and distribution volume, was 50% and 10%, respectively in the conventional dosing regimen, and was 24.5% and 10%, respectively, in the optimal dosing regimen. Using the optimal covariate model (95% confidence interval), clearance and distribution volume were: 5.36 L/kg (4.64 to 6.08) and 18.7 L (16.5 to 20.9), respectively. With the conventional dosing regimen, interindividual variability, for clearance and distribution volume, was 50.0% and 10%, respectively. Based on the optimal dosing regimen (95% confidence interval), amikacin clearance and distribution volume were estimated to be 7.22 L/kg (6.73 to 7.71) and 22.2 L (21.2 to 24.2), respectively. Interindividual variability was reduced to 24.5% and 10% for the clearance and distribution volume, respectively.

Monte Carlo simulations (N = 1,000) were used to evaluate the effectiveness of these dosing regimens in achieving the pharmacodynamics target rates. In the conventional dosing regimen, the probability achieving target rates was 100% of children, for MIC values of 0.5 to 2 μg/ml. However, this dosing regimen failed (< 40%) to achieve the pharmacodynamic target rates of children infected by organisms with a MIC = 8 μg/ml. To address this issue, new (optimal) dosing regimens were proposed to achieve the pharmacodynamic target rates for organisms with an MIC > 4 μg/ml, in at least 90% of children. This optimal dosing regimen consisted of doses (≥ 25 mg/kg) and intervals among doses of 6 to 24 hours. This optimal dosing regimen led to the pharmacodynamic target rates attainment rates in 100% of children, infected by organisms with an MIC ≥ 4 μl/ml, at the end of the first day of treatment.

Alhadab *et al.* [52] performed pharmacokinetic-pharmacodynamic and simulation analysis to evaluate amikacin dose of 15 mg/kg once-

Table 6. Amikacin pharmacokinetic parameters were obtained for conventional and optimal regimens. Amikacin was intravenously infused, at a dose of 15 mg/kg once-daily, to 70 burn children aged 4.9±3.9 years. Figures are the median, percent relative standard error, and Shrinkage value, by Alqahtani *et al*. [50]

	Conventional regimen		Optimal regimen		
Parameter	**Median**	**RSE%**	**Median**	**RSE%**	**Shrinkage (%)**
Clearance (L/h)	0.86	9	1.2	7	---
Distribution volume (L)	0.99	8	6.5	4	---
Interindividual variability for clearance	56.9	11	35.5	10	Shrinkage=3
Interindividual variability for distribution volume	73.6	18	22.6	16	Shrinkage=8
Residual variability	28.9	7	27.4	6	Shrinkage=9

Table 7. Results are obtained for optimal amikacin regimen. Amikacin was intravenously infused at a dose of 16 mg/kg (range, 13 to 20) every 8 hours, to 70 burn children aged 4.5 years (range, 2.0 to 10.0). Figures are the median, percent root mean error, percent coefficient of variation, and 95% coefficient interval, by Yu *et al*. [51]

	Optimal covariate model				Bootstrap (N=1,000)	
Parameter	**Median**	**%RSE**	**%CV**	**95%CI**	**Median**	**95%CI**
Cl (L/h)	7.22	3.43	---	6.73 - 7.71	7.21	6.71 - 7.69
DV (L)	22.7	3.31	---	21.2 - 24.2	22.9	21.0 - 26.1
BSV on Cl	0.06	25.2	0.0304-0.0598	0304-0.0898	0.062	0.0306 - 0.110
BSV on DV	0.01	---	---	---	0.010	---
RUV: (SD)	3.23	37.5	1.80	0.858 - 5.60	3.05	0.1.44 - 5.60
URV: % CV	0.0366	25.1	19.1	0.0186-0.0547	0.0416	0.0226 - 0.108

Cl=clearance. DV=distribution volume. BSV=between subject variability. RUV=residual unexplained variability. SD=standard deviation. %RSE=percent root mean square. %CV=percent coefficient of variation. 95%CI=95% confidence interval.

Table 8. Amikacin was intravenously infused to 70 burn children aged 4.5 years (range, 2.0 to 10.0). Doses were: 20, 16, and 12.5 mg/kg, and the respective intervals among doses were: 6, 8, and 12 hours. Figures are the median and (interquartile range), by Yu *et al*. [51]

Optimal regimen	Age (years)	Weight (kg)	Peak concentration (μg/ml)	Trough concentration (μg/ml)
20 mg/kg q6h (N=29)	2.0 (1.5 – 5.0)	15.5 (11.7 – 20.0)	32.2 (28.2 – 37.8)	2.7 (1.90 – 3.8)
16 mg/kg q8h (N=29)	7.0 (4.0 – 11.0	27.5 (20.0 – 50.0)	31.5 (26.2 – 37.7)	1.7 (1.2 – 3.5)
12.5 mg/kg q12h (N=11)	14.0 (1.71 – 15.0)	60.0 (11.0 – 64.0)	28.2 (25.9 – 35.3)	2.3 (1.5 – 3.5)

q6h=every 6 hours, q8h=every 8 hours, q12h=every 12 hours.

daily in 34 Egyptian cancer children aged, 3.5 years (range, 1 to 18), and weighing 25 kg (range, 8 to 70), in order to determine optimal dosing regimen. These children were infected by Pseudomonas aeruginosa having an MIC_{90} of 4 to 8 μg/ml for amikacin. A dose of 15 mg/kg was intravenously infused once-daily. Pharmacokinetics were best fitted by a two-compartment model with firs-order elimination. Median values of peak and trough concentrations (μg/ml) were 23.7 (range, 8.69 to 27.7), and 0.044 (range, 0.0075 to 2.70), respectively. The probability of target attainment rates of amikacin (Cmax/MIC ≥ 8) was estimated at the end of infusion, and trough concentration was measured at 24 hours from the start of the next infusion. The calculated probability target attainment rates for an Cmax/MIC ≥ 8 was zero for MIC_{90} of 4 and 8 μg/ml. Amikacin unbound serum concentration was below the target concentration of 10 μg/ml. Pharmacokinetic parameters were allometrically scaled to a 70 kg person. Mean clearance and distribution volume were 11.1 L/h/70 kg and 30.2 L/70 kg, respectively, with a relative standard error of 10% and 21%, respectively. Monte Carlo simulation results suggested that amikacin at a dose of 15 mg/kg once-daily is safe, but suboptimal, in these cancer children. Using the empirical Bayesian estimates, and percent unbound serum amikacin, not a single child achieved the target Cmax/MIC of ≥ 8. The probability of target attainment rates were obtained with administration of larger doses once-daily. The rationale for once-daily dosing is to maximize bactericidal effects driven by Cmax/MIC, to prolong postantibiotic effects, and to allow a longer time to excrete amikacin from the body, leading to lower trough concentration. An amikacin dose of 60 mg/kg, administered once-daily, is expected to achieve the efficacy attainment target rates of an Cmax/MIC ≥ 8 in 80% of children weighing 8 to 70 kg, with an probability and safety target of < 10 μg/ml trough concentration in almost children. Increase of amikacin dose, from 20 to 40 mg/kg once-daily, is recommended in these cancer children.

Amikacin ototoxicity and nephrotoxicity in infants and children

Abdel-Hady *et al.* [53] compared efficacy and safety, in 30 infants, aged ≥ 30 days, weighing ≥ 2,500 gram, with a postmenstrual age of ≥ 36 weeks, and with suspected or proven sepsis caused by gram-negative bacteria. Amikacin was intravenously infused at doses of 15 mg/kg once-daily (group 1, N = 15) and 7.5 mg/kg, twice-daily (group 2, N = 15). Infants of group 1 achieved trough concentration < 10 μg/ml, but 2 infants had amikacin trough concentration > 10 μg/ml, whereas children of group 2 had trough concentration was > 10 μg/ml. However, no significant difference was found in the efficacy and ototoxicity, between the children of the two groups.

Poblano *et al.* [54] assessed the relationship between amikacin serum concentration and the central conduction time in brainstem auditory evoked potentials, within therapeutic amikacin serum concentration, in 35 infants treated with amikacin therapeutic doses. Twenty-four infants were not treated with amikacin and served as controls. No alteration of the two brainstem auditory evoked potentials were found in both groups of children.

Endo *et al.* [55] performed therapeutic drug monitoring analysis in 20 infants, whose postmenstrual aged and birth-weight were 30±4 weeks and 1,280±809 gram, respectively. Amikacin was intravenously infused, at a dose of 14.1±2.6 mg/kg once-daily, and peak and trough concentrations (μg/ml) were: 29.1±7.5, and 7.6±6.9, respectively. Ototoxicity was observed in 4 infants, 3 of whom had amikacin trough concentration ≥ 10 μg/ml. After categorizing infants into two groups using a trough concentration of 10 μg/ml cut-off value, infants with amikacin trough concentration ≥ 10 μg/ml experienced ototoxicity.

Langhendries *et al.* [56] performed an investigation for assessing the tolerance in the one-and twice-daily dosing regimens in 22 infants with a postmenstrual and postnatal ages of ≥ 34 weeks and ≤ 2 days, respectively. Amikacin was intravenously infused at a dose of 15 mg/kg once-daily (N = 10) and twice-daily (N = 12) and was co-administered with ampicillin (50 mg/kg) twice-daily. Plasma concentration was measured on days 1, 3, 5, and 7 of treatment. Glomerular dysfunction was assessed by creatinine clearance and tubular injuries by urinary excretion of the following proteins: retinol binding protein, β-2-microbulin, clara cell protein (P1), gamma-microalbumin and the following enzymes: N-acetyl-D-glucusaminidase, alkaline phosphate, alanine aminopeptidase, gamma-glutamyltransferase, and total phospholipids in the urine. Ototoxicity was assessed by brainstem auditory evoked potentials. All infants had normal glomerular function normal assessed during the first days of life. Protenuria did not increase, but enzymuria, and total phospholipids concentration increased during the treatment, in both dosing regimens. Brainstem auditory evoked potentials were not significantly different between both amikacin treatment schedules. These authors concluded that, in absence of more toxicity, once-daily dosing regimen is preferred in view of its potential advantages.

Thirty-five infants with postmenstrual age of 39.0±3.5 weeks, and weighing 2,180±890 gram, were treated with amikacin at a dose of 7.5 mg/kg twice-daily. Parini *et al.* [57] assessed ototoxicity by auditory tests which were performed at 14.2 to 30.0 months postmenstrual age by cross-checking behavioural with brainstem audiometry. Only one infant was found with a mild hearing loss, which, however, could not be attributed to treatment. Nephrotoxicity was determined both by monitoring serum creatinine concentration and the urinary elimination of the lysosomal enzyme N-acetylglucosaminidase. No significant difference was found in serum creatinine concentration between the group investigated and a control group of untreated infants. A transient elevation of N-acetylglucosaminidase urinary excretion was found in one infant. These authors concluded that this dosing regimen causes a subclinical and reversible tubular damage in infants on the first days of life, despite high serum concentration.

Amikacin sulphate dose of 15 mg/kg once-daily was administered to 21 febrile children with neutropenia and cancer for 9±3 consecutive days [58]. Peak and trough concentrations ranged from 13 to 32, and < 2 μg/ml, respectively. Renal toxicity was assessed in two children (9.5%)

and were extremely mild. Two additional children (16.5%) experienced mild, transient, unilateral, high-frequency hearing loss. The lack of serious renal and auditory impairment suggests that children are at less risk than adults when they are treated with amikacin.

Amikacin therapeutic monitoring in infants

Fifty-two term infants with gestational, postnatal ages, and birth-weight of 38.7±1.1 weeks, 2.1±1.1 days, and 2,705±480 gram, respectively, and 51 preterm infants with gestational, postnatal ages, and birth-weight of 32.2±2.1 weeks, 1.4±0.8 days, and 1,908±480 gram, respectively, were treated with amikacin [59]. Amikacin dose of 15 mg/kg was intravenously infused once-daily for 7 to 10 consecutive days to all infants. Amikacin was co-administered with cefotaxime for treating infections caused by Escherichia coli, Klebsiella pneumoniae, and Enterobacter species. Trough and peak concentrations were measured 72 hours after dosing and 30 min after the end of infusion. Amikacin serum concentration correlated with serum creatinine concentration (r^2= 0.480; P-value < 0.05). Preterm infants had significantly higher median serum concentration (μg/ml) of 11.33 (range, 1.50 to 42.6) than term infants (range, 2.81 to 31.0). Serum concentrations were within the therapeutic interval. The frequency of toxic amikacin concentration was significantly higher in preterm (32, 61.5%) than in term infants (11, 21.1%). Seventy-two hours after dosing, serum concentration (μg/ml) was 61.4±22.8 and 76.0±28.9 in term and in preterm infants respectively (P-value = 0.02). Twelve preterm infants (23.1%) and 5 term infants (9.6%) had amikacin subtherapeutic concentrations. These results show that the above retorted amikacin dose causes toxic amikacin serum concentration in preterm infants. Thus, amikacin dosing protocol should be individualized on the basis of body weight. Amikacin doses of 7.5 and 10 mg/kg once-daily should be administered to preterm and term infants, respectively. Amikacin therapeutic monitoring is an important tool to avoid toxic amikacin in infants.

Myers *et al.* [60] measured amikacin serum concentration in 37 infants with postmenstrual, postnatal ages, and birth-weight of 36 weeks (range, 30 to 42), 2.2 days (range, 1 to 10), and 2,499 gram (range, 780 to 4,495) for determining effects of the postmenstrual age, birth-weight, and hypoxemia, on amikacin serum concentration. Amikacin was intravenously infused at a dose of 7.5 mg/kg twice-daily in 22 infants, and 15 infants received this dose intravenously and intramuscularly. Amikacin was co-administered with ampicillin (100 mg/kg) to treat infections caused by gram-negative bacteria. Peak serum concentrations (μg/ml) ranged from 9.0 to 36.0, with a mean of 17.7. These authors did not measure amikacin trough concentration. There was no difference between amikacin peak concentration in younger, older, and hypoxemic infants. In contrast, half-life (hours) was significantly longer in preterm (5.9±2.3, N = 19) than term (4.5±1.6, N = 17) infants (P-value < 0.05), whereas hypoxemia did impair amikacin half-life. These results indicate half-life is prolonged in preterm than in term infants.

Rusconi *et al.* [61] assessed the effect of postmenstrual and postnatal ages, and respiratory distress syndrome on amikacin serum concentration, in 39 infants, with a postmenstrual of 28.5 to 42 weeks, in the first week of life. Amikacin was administered intramuscularly at a dose of 7.2 mg/kg twice-daily, for an average period of 6.5 days, and serum concentration was monitored through treatment. Both postmenstrual and postnatal ages influenced serum concentration. Respiratory distress syndrome, assessed during the first week of life, yielded a strong accumulation in serum. Lower serum concentration was observed in infants with retarded intrauterine growth. Peak concentration did not correlate with vital or clinical data, probably because of the variability in drug absorption from the intramuscularly injection site. Maturation of renal function yielded a decrease in serum concentration, and the distribution volume decreased, in the first days of life, because the decrease of body fluid compartment occurring in this period of life.

Want *et al.* [62] assessed interindividual variability of serum level in 22 infants with a postmenstrual age of 26 to 34 weeks. Amikacin was administered intramuscularly at a dose of 7.5 mg/kg twice-daily. Peak concentration, measured one hour after injection, had a wide interindividual variability, and averaged at 18.2 μg/ml. Trough concentration varied considerably in individual infants from day to day, but amikacin did not accumulate in serum. Adverse-effects caused by amikacin treatment were found associated with decrease of renal and hepatic functions.

Bacteria resistance to amikacin

Hurley *et al.* [63] studied 27 amikacin-resistant isolates of Pseudomonas aeruginosa from children with cystic fibrosis to determine the mechanism of amikacin-resistance. The absence of aminoglycoside-modifying enzymes in these isolates was inferred from the failure of DNA probes for 16 candidate aminoglycoside-modifying enzymes to hybridize with DNA harvested from these isolates, in addition, it was observed an uniform reduction in susceptibility to a panel of aminoglycosides. In 8 of the 26 isolates that were resistant to amikacin at high levels (MIC ≥ 250 μg/ml), plasmids were not detected. Ribosomes of these isolates were sensitive to amikacin in studies of protein synthesis by cell "ghosts". These data suggest that impermeability is the mechanism of amikacin-resistance in isolates of Pseudomonas aeruginosa in children with cystic fibrosis. Recognition of this mode of resistance may be difficult, as some isolates appeared to be borderline susceptible, when tested against aminoglycosides, other than amikacin, or had zone diameters that overlapped those obtained with amikacin-susceptible isolates.

Gram-negative isolates obtained from blood and cerebrospinal fluid, were monitored for 1 year before and 1 year after the introduction of first-line aminoglycoside in a busy paediatric department which switched amikacin to gentamicin [64]. In the general paediatric wards, amikacin was replaced to gentamicin. 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 carriage in aminoglycoside usage, the resistance to amikacin of nosocomial acquired gram-negative infections increased from 7.6 to 27.7% (P-value < 0.001), and the resistance to gentamicin decreased from 71.2 to 60.2% (P-value = 0.07). The increase in amikacin resistance of gram-negative bacilli, other than Serratia species, has persisted for more than 1 year after of amikacin. These effects were observed in two sections of the paediatric department and may be related to the more intensive usage of aminoglycosides in the neonatal unit.

Hammerberg *et al.* [65] determined the prevalence of aminoglycosides-resistant Staphylococcus aureus and coagulase-negative staphylococci before and after the introduction of amikacin as the sole aminoglycoside used in the burn unit, and neonatal intensive care unit. Pharyngeal or endotracheal 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 all neonatal intensive care unit 30 months after amikacin introduction. A total of 2,613 strains of coagulase-negative

staphylococci, and 316 strains of Staphylococcus aureus, were obtained from 916 patients. During the course of the study, 17% of coagulase-negative staphylococci and 12% of Staphylococcus aureus strains became resistant to amikacin, 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 period, this value dropped to 40%, and 48% of the strains had become resistant to all three aminoglycosides. Resistance to aminoglycosides, including amikacin, developed 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.

Two multiresistant Klebsiella pneumoniae strains isolated from cerebrospinal fluid of infants were analyzed for their plasmid content [66]. Two of plasmids harboured by these strains, pJHCMW1 gene (75 kilobase pairs), carried genetic determinants for amikacin resistance. These plasmids also encoded resistance to kanamycin, tobramycin, and ampicillin which could be transferred to Escherichia coli by conjugation. Extracts from transconjugant derivatives carrying pJHCMW4 gene produced an acetyltransferase activity that acetylated all three antibiotics. Transconjugant derivatives carrying pJHCMW1 gene were encoded by both acetylating and phosphorylating activities, Southern blot hybridization analysis indicated a considerable DNA homology between these two plasmids.

Discussion

Amikacin spectrum of activity is the broadest of all aminoglycosides. Amikacin is active against most strains of Serratia, Proteus, and Pseudomonas aeruginosa as well as most strains of Klebsiella, Enterobacter, and Escherichia coli that are resistant to gentamicin and tobramycin, and is rapidly bactericidal. Bacterial killing is concentration depended: the higher concentration, the greater the rate of bacterial killing. The inhibitory activity of aminoglycosides persists after the serum concentration has fallen below the MIC, postantibiotic effect. Amikacin is frequently used in combination with a cell wall-active gent (β-lactam or glycopeptides) for the therapy of serious infections. The three rationales for this approach are: (1) to expand the empiric spectrum of activity of the antimicrobial regimen, (2) to provide synergistic bacterial killing, and (3) to prevent the emergence of resistance to the individual agents [3]. Although amikacin transfers significantly the placenta, no ototoxicity and nephrotoxicity have been documented in the foetus [1]. Monitoring amikacin serum levels has been recommended when it is administered more than 48 hours in infants [2]. This antibiotic is safe and efficacy in infants and children [8-10]. Amikacin recommended doses are 15 mg/kg once-daily and 7.5 mg/kg twice-daily in infants, and 20 to 40 mg/kg once-daily in children. Amikacin dosing once-day is preferred than twice-daily, because reduces trough concentrations, thus decreasing risks of toxicity, and increase peak levels, thus improving therapeutic efficacy [15-22]. Amikacin causes limited ototoxicity and nephrotoxicity infants and children [53-57] and poorly concentration has been observed in bronchial effusion [24-26] in skeletal muscle and fat tissue [27]. Because of its polar nature, amikacin poorly penetrate into the cerebrospinal fluid [28-30]. After an amikacin mean dose of 15 mg/kg, administered by lumbar puncture, mean peak concentration was 35.7 and 1.08 μg/ml in serum and cerebrospinal fluid, respectively, and the cerebrospinal fluid to serum ration was 0.03 [28]. Pharmacokinetics has been extensively studied in infants [32-34] and children [35-37]. Half-lives are 6 hours in infants, during the first weeks of life [23], and 1.9 hours in children up to 6 years [45]. Pharmacokinetic parameters remarkably vary in infants [46, 47] and children [48]. Burn [44, 51], cancer [44, 51], and renal impairment [45] have an important impact on pharmacokinetics. Optimisation of amikacin dosing regimen has been recommended in infants [49] and children [50-52]. Optimal dosing regimen in preterm infants consists of 7.5 mg/kg amikacin every 15 and 12 hours, in infants aged < 7 days and > 7 days, respectively [48]. In children, amikacin optimal dosing regimen was definite as that yielding the ratio Cmax/MIC ≥ 8 [50-52]. The probability of reaching this ratio was obtained with 16 mg/kg every 8 hours in [51] and with 20 to 40 mg/kg once-daily [52]. Because of amikacin narrow therapeutic interval, monitoring of serum levels has been recommended in infants [59-62]. Such a monitoring is of particular importance in preterm infants, who have long serum half-life, and a remarkable interindividual variability in serum concentration. Some bacteria may become resistant to amikacin [63-66]. Hurley *et al.* [63] described the mechanism of amikacin resistance in strains of Pseudomonas aeruginosa. Some of these isolates were resistant to amikacin because had high MIC ≥ 250 μg/ml, in addition, impermeability is another mechanism of amikacin-resistance in isolates of Pseudomonas aeruginosa. In conclusion, amikacin is rapidly bactericidal; its spectrum of activity is the broadest of all aminoglycosides. This antibiotic is active against most strains of Serratia, Proteus, and Pseudomonas aeruginosa as well as most strains of Klebsiella, Enterobacter, and Escherichia coli that are resistant to gentamicin and tobramycin. The recommended doses of amikacin are 15 mg/kg once-daily and 7.5 mg/kg twice-daily in infants and 20 to 40 mg/kg once-daily, in children. The once- is preferred than the twice-daily dosing regimen because it yields lower trough concentration, thus reducing risks toxicity, and higher peak concentration, thus improving therapeutic efficacy. Amikacin half-lives are 6 and 1.9 hours, in infants in the first week of life, and in children aged up to 6 years, respectively. The interindividual variability of pharmacokinetic parameters is remarkable, thus monitoring serum concentration is recommended, especially in preterm infants, who have a long half-life, and remarkable interindividual variability. Optimisation of amikacin dosing regimen has been recommended in infants and children. Limited ototoxicity and nephrotoxicity has been observed in infants and children treated with therapeutic doses of amikacin. Infant maturation is associated with a reduction of half life, and with an increase of clearance. Burn, cancer and renal impairment have an important impact on pharmacokinetic parameters. Some bacteria may become to amikacin.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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