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REVIEW

Clinical pharmacology of gentamicin in neonates: regimen, toxicology and pharmacokinetics

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Gentamicin is an aminoglycoside antibiotic. It kills bacteria by inhibiting protein synthesis and to some extent by lysing the cell envelope. Gentamicin is frequently the first choice drug because of its reliability, but also because of the long experience with its use. In combination with β-lactam antibiotics it is recommended for the treatment of sepsis or pneumonia and is active against P. aeruginosa, Enterobacter, Klebsiella and Serratia. However, gentamicin is ototoxic and nephrotoxic. The human mitochondrial genetic variant m.1555A > G has been reported to be an important cause of non-syndromic hereditary hearing dysfunction and may cause permanent hearing loss. Even short courses of gentamicin therapy in healty newborn infants can lead to abnormalities of auditory function. It is active against very resistant bacteria at peak concentrations (> 10 mg/l) that are high enough to be potentially toxic. For safe therapeutic efficacy, peak plasma concentrations of gentamicin should range from 4 to 10 mg/l; but trough concentrations, immediately before a new drug administration, must be lower that 2 mg/L to avoid toxic effects. Pharmacokinetic parameters vary considerably in infants. Half-life ranges from 5.4 to 10.0 hours, clearance 0.50 to 1.71 ml/h/kg and distribution volume from 0.4 to 0.7 l/kg. Preterm infants have a longer half-life than full-term infants. Thus, it is mandatory to monitor gentamicin serum concentrations whenever infants are treated for 48 hours or more.

KEYWORDS: Gentamicin; Neonate; Nephrotoxicity; Ototoxicity; Pharmacokinetics, Toxicity.

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INTRODUCTION

Gentamicin is a naturally occurring substance produced by the environmental gram-positive bacteria Micromonospora and was first isolated in 1963.[1] Absorption from the gut is too limited to disallow maternal use during lactation. Gentamicin is passively filtered unchanged by glomerulus and concentrated in the urine. In healthy infants the half-life decreases by more than 50% over the first 7 to 10 days after birth. Renal tubular damage is progressive with time and can even produce a Bartter-like syndrome. Cochlear impairment is uncommon in young children, but gentamicin can cause balance problems as well as high-tone deafness, and these can become permanent if early symptoms go unrecognized. Blood levels should always be measured in order to minimize this risk. It is very important to avoid simultaneous treatment with furosemide and to try to stop treatment after 7 to 10 days.

Gentamicin is an important antibiotic for the treatment of many serious gram-negative aerobic bacillary infections. It kills bacteria by inhibiting protein synthesis and to some extent by lysing the cell envelope. It is the aminoglycoside of first choice because of its reliable activity against most resistance gram-negative aerobes and because of the long experience with its use. The major indications for gentamicin are in combination with other antibiotics (e.g., β-lactams) to treat serious aerobic bacterial infections. Gentamicin in combination with a β-lactam antibiotic is recommended for the treatment of pneumonia or sepsis, where multi-drug-resistant gram-negative organisms such as P. aeruginosa, Enterobacter, Klebsiella and Serratia may be the causative pathogen and/or the consequences of failing to provide initially active therapy.[2] Gentamicin is only effective against many bacteria when its serum level is

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high enough to be potentially toxic. High concentrations (at least eight times the minimum inhibitory dose) enhance the drug's bactericidal effect. However, it is important to note that Gram-negative organism stop taking up the drug after an hour and only do so again 2-10 hours later. Therefore, any repeat administration within this time interval may prove to be ineffective. Serious toxicity is predominantly seen with treatment longer than 7-10 days where there are sustained high trough serum levels and/or co-exposure to other ototoxic drugs. In infants with normal renal function, treatment is optimized, and adverse effects are minimized, by following a once a day ('high peak, low trough') policy. An increased number of studies have now suggested that this is the correct strategy to adopt in infants and children. When aminoglycosides are given more than once a day in children, the serum level will remain sub-therapeutic for many hours if an initial loading dose is not given because of the larger distribution volume.

BIBLIOGRAPHIC SEARCH

The bibliographic search was performed using PubMed database as search engine; April 2015 was the cutoff point. The following key words "gentamicin activity neonate", "gentamicin toxicology neonate" and "gentamicin pharmacokinetics neonate" were used. In addition, the books Neonatal Formulary[1] and NEOFAX by Young and Mangum[3] were consulted.

RESULTS

Regimen of gentamicin

Several dosage schedules have been suggested for newborn infants: (a): 3 mg/kg once daily for preterm infants < 35 weeks of gestation; (b): 4 mg/kg once daily for newborns > 35 weeks of gestation; (d): 5 mg/kg daily in two divided doses for neonates with severe infections; and (e): 2 to 2.5 mg/kg every 8 hours for children up to 2 years of age.[4,5]

However, two basic strategic approaches should be adhered to (i): infants with less than 32 weeks gestation should be treated with 3 mg/kg gentamicin once every 36 hours over the first week of; (ii): for all other infants a single dose once every 24 hours is recommended, provided that renal function is not poor. A strategy to individualize treatment in very immature infants (≤ 28 weeks gestation) may be followed by measuring the gentamicin level 22 hours after a single dose: the timing of the next dose can be then calculated according to the measured level. Gentamicin is frequently used in infants undergoing therapeutic hypothermia. These infants typically have renal impairment, close monitoring is mandatory, and dose adjustments are frequently needed. A 4 mg/kg dose and a 36 hourly regimen is seen as best for these infants.

Monitoring

Serum concentrations of gentamicin must be monitored when treatment extends for more than 48 hours. A reading (peak) concentration must be obtained 30 minutes after end of infusion, and a trough concentration immediately prior to the next dose. Peak plasma concentrations range from 4 to 10 mg/l. Trough concentrations should be less than 2 mg/l. When treating patients with serious infections or significantly changing fluid or renal status measuring the serum concentrations 24 hours after a dose is highly recommended.

Ototoxicity of gentamicin in neonates

Gentamicin is routinely used in neonatal intensive care to treat bacterial infection. However, this drug is ototoxic. Hearing loss is more prevalent in infants born before 32 weeks of gestation than in term neonates. However, harmful effects occur in all infants. Blood levels should be maintained within the standard therapeutic range. But it must be kept in mind that for individuals with the mitochondrial genetic variant m.1555A > G, permanent hearing loss can occur even when drug levels are within standard therapeutic limits. Bitner-Glindzicz et al.[6] investigated the burden that the m.1555A > G mutation represents to deafness in very preterm infants. These authors performed a case control study of children born at less than 32 completed weeks of gestation with confirmed hearing loss. Risk associated with gentamicin, m.1555A > G and other co-morbid risk factors were evaluated using conditional logistic regression. They conclude that genetic testing during pregnancy, postnatal testing prior to drug administration, or the use of an alternative first line antibiotic should be considered. They also note that detailed perinatal data collection will also allow greater definition of the causal pathway of acquired hearing loss in very prematurely born children.

Cooper et al.[7] examined hearing loss in 528 infants receiving a high doses of gentamicin. Neonates were clustered into two groups, with less than or more than 1500 g birth weight. Gentamicin was administered at the dose of 4 mg/kg every 48 hours if the neonate's birth weight was < 1,250 g or if the neonate was receiving indomethacin; otherwise, the dosing interval was 24 hours. Otoacustic emission data were monitored. In the very low birth neonates, otoacustic emission failure was 34.1% (29/85), whereas in non low birth weight infants the rate was (9% [40/443], p = 0.001). Among the lower birth weight neonates, no association between serum gentamicin concentration and otoacustic failure could be determined. In contrast, in the higher birth weight infants each 1 mg/l increase in gentamicin Cmax was associated

with an increased risk of otoacustic failure. Further, if the gentamicin Cmax exceeded 10 mg/l an additional increased rate otoacustic failure was observed.

Mutations in the 12S rRNA gene have been associated with aminoglycoside-induced ototoxicity. Johnson et al.[8] examined whether such mutations are associated with aminoglycoside-induced ototoxicity. A total of 378 infants with birth weight < 2500 g were treated with gentamicin during their stay in the neonatal intensive care units. Mutations in the 12S rRNA gene were observed in 4 infants (0.9%), all of whom were treated with gentamicin. However, they showed no evidence of hearing loss. But low birth weight was one risk factor related to the presence of failing a hearing assessment.

The treatment of acute hematogenic osteomyelitis requires high concentrations of gentamicin administered locally for 3 weeks. Kos et al.[9] evaluated the effects of local gentamicin on auditory function. Gentamicin sponges were implanted in 20 neonates with hematogenic osteomyelitis. Brainstem-evoked auditory potentials were examined before and during the first 3 weeks, and 6 to 11 months after gentamicin implantation. Gentamicin serum concentrations were examined on the 1st, 4th, 8th and 16th day after implantation, but never exceeded the upper therapeutic range limit. Brainstem-evoked potentials were normal in 15 of 16 children before treatment and in 14 of 16 children after treatment. Locally applied gentamicin resulted in very low serum concentrations (close to the minimal therapeutic levels) and change in brainstem-evoked potentials suggest that there was no inpairement of auditory function occurred.

Aust[10] and Aust & Schneider[11] reported two studies on the vestibulotoxicity and ototoxicity of gentamicin in newborns at risk. In study 1, out of 8,333 children examined for hearing disorders, 134 (1.6%) had received previous gentamicin treatment: only eight of these suffered from various extents of sensorineural hearing impairment, and all had a history of other risk factors of hearing loss (e.g., perinatal asphyxia, acidosis, icterus gravis, or meningitis). In study 2, thirty children (mean age, 13.2 months) with normal hearing had received gentamicin during the newborn phase, and 30 healthy children of similar age without previous gentamicin treatment were examined for vestibular function. Neither in the number of spontaneous eye movements nor in the means of the nystagmus parameters of the rotatory test did the data show any significant difference between the groups. The results indicate that gentamicin in controlled therapeutic doses has a less ototoxic and vestibulotoxic effect in newborns than it does in older children or in adults.

Kohelet et al.[12] found a less favorable outcome regarding the effect of gentamicin in 7 infants on the first day of life whose mothers had rupture of membranes and maternal fever; these were compared with 9 healthy term infants to determine whether this drug induces alterations in the auditory pathway. The auditory pathway was investigated on the 3rd day of life by analyzing brainstem auditory evoked potentials elicited by click stimuli presented to the infants' ears. Peak and trough gentamicin levels all fell within the recommended therapeutic range. But latencies of various components were significantly prolonged in the gentamicin group, suggesting impairment of the central component of the auditory pathway.

Colding et al.[13] performed audiometry tests at four years of age in 69 of 105 surviving children who had received continuous intravenous infusion of gentamicin during neonatal intensive care. A hearing loss of 2 dB was found in 2 of them (3%), corresponding to that shown in other studies of survivors following neonatal intensive care, as described above.

Finitzo-Hieber et al.[14] report the results of a four-year follow-up study initiated in 1970 on the long-term effects of gentamicin and kanamycin use in newborn infants. Audiometric, vestibular, and psychometric evaluations were performed on gentamicin-treated, kanamycin-treated, and untreated, matched control infants and children. No substantial sensorineural hearing loss or vestibular dysfunction was identified in these patients that could be attributed to aminoglycoside therapy.

In summary, gentamicin can be used in neonates with very rare effects on hearing, provided that monitoring precautions are rigidly adhered to.

Nephrotoxicity of gentamicin in neonates

It is a well-established fact that gentamicin is a nephrotoxic agent and that this applies to neonates. Tugay et al.[15] determined the acute effects of trough and peak levels of gentamicin on the values of serum creatinine, urine albumin/urine creatinine ratio, fractional excretion of sodium and potassium, and urine calcium/urine creatinine ratio in 61 preterm neonates treated with the antibiotic. Measurements were made at the start of therapy, on the day of the third gentamicin dose and 48-72 hours after the cessation of gentamicin therapy. Peak and trough levels were within the therapeutic in 56 (91.8%) and 39 (63.9%) of the preterm neonates, respectively; high trough (> 2 mg/dl) and peak (> 10 mg/dl) levels were recorded in five (8.1%) and 11 (18%) cases, respectively. Trough and peak levels correlated positively with serum creatinine, urine albumin/urine creatinine ratio, fractional excretion of sodium, fractional excretion potassium and urine calcium/urine creatinine values.

Giapros et al.[16] determined the acute effect of gentamicin administration on renal electrolyte handling in 23 preterm and full-term infants. Serum and urine electrolytes were measured before and immediately after gentamicin infusion and on the 1st, 3rd, 4th, and 7th day of treatment. They report that therapeutic doses of gentamicin

result in urinary loss of sodium, calcium and magnesium in neonates immediately after the infusion of gentamicin and note that these electrolyte changes may be of clinical importance, especially for sick preterm neonates.

Heimann[17] studied kinetic parameters of gentamicin in 14 infants, using an open three-compartment body model. Compared to normal adults: (a) at lower glomerular filtration rates the β-elimination is longer in the newborn infant while the γ-elimination phase; (b) the calculated drug accumulation in the deep compartment (kidney) under steady state conditions is lower in newborns; (c) the excretion of urinary enzymes of tubular origin are lower in the newborns. The data indicate that there may be a lower renal accumulation of aminoglycosides in newborn infants, which can be explained by the morphometric and functional characteristics of the newborn kidney.

Tessin et al.[18] treated 13 newborn infants, 8 term and 5 preterm (gestational age between 31 and 36 weeks), with gentamicin and ampicillin or cloxacillin. The dosage of gentamicin was carefully monitored by serum concentration assay. Unitary alanine aminopeptidase, urinary β 2-microglubulin, serum urea and serum β 2-microglobuline were measured during and after the end of treatment to detect signs of renal toxicity. Levels of urinary aminopeptidase increased in 12 of them, indicating damage to the cells of the proximal tubuli. Changes in urinary β 2-microglobulin followed the normal physiological course seen in neonates after birth.

Urinary excretion of the tubular enzymes N-Acetyl-β-D Glucosaminidase (NAG) and β-amyloid precursor protein (APP) was investigated by Colding et al.[19] during gentamicin treatment in 105 newborn infants.[19] The urinary excretion of NAG was 92% higher during gentamicin treatment vs. non-treatment periods. However, the long-term effect of the higher excretion of NAG and AAP in newborn and adult patients during aminoglycoside treatment is unknown.

Pharmacokinetics of gentamicin in neonates

The kinetic parameters for all the studies referenced here are summarized in table 1.

Lulic-Botic et al.[20] compared gentamicin pharmacokinetics among neonates born small - vs. appropriate-for gestational. Gentamicin half-life was significanlty longer and clearance lower in small-for gestational age, whereas the distribution volume was similar. In small-for-gestational age peak and trough concentrations were 7.7 (range 5.5-8.5) and 1.2 (1.1-1.6) mg/mL, respectively. In appropriate for gestational age the peak and trough concentrations were 7.6 (6.2-8.6) and 1.1 (0.8-1.6) mg/mL, respectively, with no significant difference between groups.

Mark et al.[21] endeavored to determine whether therapeutic hypothermia in newborns with hypoxic ischemic encephalopathy affects gentamicin pharmacokinetics. Half-life was significantly longer, clearance significantly lower and distribution volume significantly smaller in hypothermic vs. normothermic infants. Therapeutic hypothermia is associated with alteration in gentamicin pharmacokinetics, reducing gentamicin clearance by 25.5%; this that may result in increased trough concentrations.

Frymoyer et al.[22] evaluated the pharmacokinetics of gentamicin in 29 full-term neonates with hypoxic ischemic encephalopathy. The dose of gentamicin was 5 mg/kg every 24 hours. Gentamicin clearance was found to be decreased in neonates with hypoxic ischemia encephalopathy vs. non-asphyxiated normothermic infants. A prolonged 36-hour dosing interval is recommended to achieve target gentamicin trough concentrations in this population.

Hoff et al.[23] determined the pharmacokinetic outcomes of a simplified, weight-based, extended-interval gentamicin dosing protocol for 644 critically ill neonates. A mean dose of 3.96 mg/kg/dose was administered every 48 hours to neonates weighing < 1,250 g at birth and every 24 hours to those weighing ≥ 1250 g. Protocol success was defined as a peak gentamicin plasma concentration of 7 to 10 mg/l and a trough concentration less than 2 mg/l. The protocol resulted in 361 neonates (56.1) achieving successful gentamicin peak plasma concentrations and 610 neonates (94.7%) achieving successful trough concentration.

Hayani et al.[24] performed a randomized trial of once-daily (11 neonates - 5 mg/kg) vs. twice-daily (15 neonates - 2.5 mg/kg) intravenous or intramuscular dosing with gentamicin for 2 to 3 days. The once-daily vs. twice-daily groups had mean steady-state gentamicin peak concentrations of 10.7 vs. 6.6 mg/l ($p < 0.05$), trough concentrations were 1.7 vs. 1.7 mg/l. Thus, the once-daily group achieved more suitable peak levels without overshooting the recommended trough levels. No nephrotoxic effects were identified in either group.

Rocha et al.[25] studied gentamicin pharmacokinetics in 68 preterm infants with a gestational age range from 24 to 34 weeks, body weight range 600 to 3,100 g. A standard 2.5 mg/kg dose of gentamicin was administered intravenously and the interval between doses was selected through patient's weight: 24-, 18-, and 12- hours intervals for weights: < 1,200, 1,200-2,000 > 2,000 g, respectively. By regression analysis weight was the strongest co-variate: gentamicin clearance and distribution volume had to be normalized. Additionally, gentamicin clearance depended on gestational age with a cut-off at 30 weeks, which allowed the division of the overall population into two subsets (< 30 and 30 to 34 weeks). The younger neonates showed a lower clearance (0.60 vs. 0.85 ml/min/kg), slightly higher distribution volume (0.5 vs. 0.4 l/kg), and a longer half-life (8.9 vs. 5.4 hours) compared with the older counterparts. On the basis of the pharmacokinetic parameters Rocha et al. suggest loading doses of 3.7 and 3.5 mg/k and maintenance doses of 2.8 mg/kg/24 hours and 2.6 mg/kg/18 hours for the two subgroups of neonates, respectively.

Table 1 - Pharmacokinetic parameters of gentamicin in neonates. The figures are the mean or the mean ± SD

Number of cases	Note	Development stage	Half-life (hours)	Clearance (ml/min/kg)	Distribution volume (l/kg)	Reference
29	SGA	Preterm	10.0	0.58	0.5	20
135	AGA		8.5	0.68	0.5	
16	Hypothermic infants	Term	9.2	0.68	0.5	21
7	Normothermic infants		6.6	0.50	0.4	
29	Hypothermic infants	Term	10.7	0.59	0.5	22
644	Preterm	Preterm	8.3	0.69	0.5	23
11	5.0 g/kg gentamicin	Preterm	8.8	0.88	0.7	24
15	2.5 x 2 g/kg gentamicin		5.4	0.69	0.46	
49	< 30 weeks	Preterm	8.9	0.60	0.5	25
	30-34 weeks	Preterm	5.4	0.85	0.4	
18	ECMO	Preterm	10.0 ± 0.7	0.70 ± 1.2	0.4 ± 0.02	26
12	Off ECMO	Preterm	5.7 ± 0.07	0.95 ± 0.07	0.6 ± 0.04	
32	**28 weeks**	**Preterm**	**10.2**	**0.53**	**0.5**	
49	**28-34 weeks**	**Preterm**	**8.9**	**0.62**	**0.5**	**27**
58	**> 34**	**Term**	**7.0**	**0.78**	**0.5**	
29	Postnatal age 6 ± 2 days	Preterm	9.3 ± 34.6	0.86 ± 0.21	0.7 ± 0.2	30
5	Postnatal age 15 ± 4 days	Preterm	5.1 ± 13.3	1.71 ± 0.17	0.7 ± 0.2	
106	PDA	Preterm	10.3	0.67	0.6	29
216	CDA		8.0	0.74	0.5	
195	Preterm and term	Preterm and term	7.2 ± 2.6	0.78 ± 0.20	0.4 ± 0.1	31
29	V-A- Bypass	Term	10.0 ± 2.4	0.16 ± 0.05 (l/h)	0.6 ± 0.1	32
29	V-V Bypass	Term	10.7 ± 3.4	0.2 ± 0.09 (l/h)	0.7 ± 0.2	32
-	Adults	-	2-3	0.82 Clcr ± 0.1	0.3 ± 0.1	37

SGA: small for gestational age; AGA: appropriate for gestational age; ECMO: extracorporeal membrane oxygenation; PDA: patent ductus arteriosus; CDA: closed ductus arteriosus; V-A- Bypass: vein-arterial bypass; V-V-Bypass: vein-vein-bypass.

Cohen et al.[26] evaluated the effects of extracorporeal membrane oxygenation on the pharmacokinetics of gentamicin in 18 infants who underwent the procedure for severe respiratory failure and received gentamicin for possible sepsis. Twelve of these patients continued to receive gentamicin after the end of extracorporeal membrane oxygenation. In patients still receiving extracorporeal oxygenation, the volume of distribution was larger, the clearance smaller and half-life longer compared to those removed from the procedure. Cohen et al therefore suggest that gentamicin and probably other aminoglycosides should be given at dose rates about 25% lower and at longer dosing intervals in patients undergoing extracorporeal membrane oxygenation therapy.

DiCenzo et al.[27] developed a gentamicin pharmacokinetic population model and once-daily dosing algorithm for 139 neonates younger than 10 days (median/range for gestational age 32/23-42 weeks; weight 1,920/470-5,000 g. The neonates were divided into three groups receiving 24-hour gentamicin regimens based on gestational age and birth weight. Total body clearance increased with the gestational age, and distribution volume was associated with the birth weight ($r^2 = 0.700$). The kinetic parameters are highlighted in table 1. The following dosing algorithm was designed to reach a therapeutic 24-hours area under the curve of 57.5 mg/l x hour) in neonates during the first 10 days of life: 24-hours gentamicin dose (mg) = (0.441 ± [0.094 x gestational age]) x birth weight.

Touw et al.[28] studied gentamicin pharmacokinetics in 12 neonates with patent ductus arteriosus and 12 infants with closed ductus arteriosus. A patent ductus arteriosus may influence renal and hepatic blood flow and hence the pharmacokinetics of drugs. No significant differences between both populations for gentamicin total body clearance were observed. Distribution volume tended to be larger and elimination rate smaller in neonates with patent ductus arteriosus. Multiple regression analysis showed (for both populations) highly significant correlations between body clearance and distribution volume vs. body weight or gestational. Although neonates with patent ductus arteriosus may have small differences in gentamicin pharmacokinetics

compared to those with a closed ductus arteriosus, this is not relevant for clinical practice taking the variability within that population into account.

In contrast, Williams et al.[29] determined the effect of patent ductus arteriosus on the pharmacokinetics of gentamicin in neonates and examined whether any particular pharmacokinetic parameter is of value as a marker of patent ductus arteriosus. The half-life, the clearance and the distribution volume were significantly different in the two groups.

Vervelde et al.[30] characterized the population pharmacokinetics of gentamicin in 34 preterm neonates on a once-daily dosage regimen of 3.0 mg/kg given intravenously every 24 hours. The gestational age was 32 ± 4 weeks. Cluster analysis showed a division into 2 subpopulations (designed 1 and 2) on the basis of postnatal age. The subpopulation 1 (n = 29) had a postnatal age 6 ± 2 days and the subpopulation 2 (n = 5) had a postnatal age 15 ± 4 days. The half-life and the clearance were significantly different, whereas the distribution volume was not statistically different in the two subpopulations.

Murphy et al.[31] studied the pharmacokinetics of gentamicin in 195 neonates. Weight, urine output, gestational age, and postconceptional age had the highest correlation with the pharmacokinetic values. Blood urea nitrogen and Apgar score were poor predictors of the pharmacokinetic values. There were not differences among patients based on race.

Bhatt-Mehta et al.[32] determined (1) the pharmacokinetics of gentamicin in term neonates on extracorporeal membrane oxygenation and compared them to reported values for similar infant population not on extracorporeal membrane oxygenation, (2) whether the pharmacokinetics of gentamicin differ between venous-venous and venous--arterial bypass, and (3) whether the pharmacokinetics of gentamicin are affected by oxygenator surface area (0.6 m^2 vs. 0.8 m^2. None of these comparisons yielded significant differences. This suggest no apparent drug adsorption onto the oxygenator membrane.

DISCUSSION

Gentamicin is an aminoglycoside antibiotic active against gram-negative aerobic bacillary infections. Among the various aminoglycosides, gentamicin is the first choice drug because the reliable activity against most resistance gram-negative aerobes and for the long experience with its use. In combination with a β-lactam antibiotic it is particularly useful against P. aeruginosa, Enterobacter, Klebsiella and Serratia. To be effective against many bacteria the serum level must be high enough to be potentially toxic (< 10 mg/l) but the trough concentrations must be < 2 mg/l to avoid toxicity. Gentamicin is ototoxic and nephrotoxic. Serious toxicity is seen after 7 to 10 days of treatment. To reduce toxicity the trough concentration must be low and therefore one administration per day is the suggested regimen. A loading dose is useful to increase the peak concentration shortly after the administration. The suggested dose is 3.0 mg/kg once daily for preterm infants, 4 mg/kg once daily for newborn > 35 weeks of gestation and 5 mg/kg daily in two divided doses for neonates with severe infection.[4,5] It is important to measure serum gentamicin concentrations when the drug is administered for more than 48 hours.

The toxicity of aminoglycosides seems less frequent in newborn infants compared to adults even though glomerular filtration rate, tubular secretion and reabsorption mechanisms are subject to adaptive processes during the neonatal period.[17] Kinetic parameters of gentamicin have been determined in infants. The β-elimination phase of gentamicin is longer in the newborn infant compared to adults. The accumulation of gentamicin in the kidney under steady state conditions is lower in newborns compared to adults. The excretion of urinary enzymes of tubular origin, namely lysosomal NAG, β-glucuronidase and the brush-border-associated APP and GGT, are lower in healthy newborn infants compared to adults. The increase of alanine aminopeptidase (AAP) during aminoglycoside therapy is less pronounced in newborn infants, especially in prematures if compared to adult values. After the end of therapy, AAP excretion decreases to normality.

Urinary alanine aminopeptidase, urinary β 2-microglobulin, serum urea and β 2-microglobuline have been measured in infants treated with gentamicin and ampicillin or cloxacillin.[18] Levels of urinary aminopeptidase increased in almost all of them of them, indicating damage to the cells of the proximal tubuli. Changes in urinary β 2-microglobuline followed the normal physiologic course seen in neonates after birth. Serum levels of urea and β 2-microglobulin did not indicate any-associated depression of glomerular filtration.

Gentamicin is mainly eliminated by glomerular filtration and excretory renal function is more affected in neonates than in adults. Half-life ranges from 5.4 to 10.0 hours in preterm neonates < 1 week of age, but from 2 to 3 hours in adults. Postnatal age is an important factor influencing the half-life and the clearance of gentamicin. At a postnatal age of 6 ± 2 days half-life and clearance are lower than in infants with a postnatal age of 15 ± 4 days.[30] This difference reflects the maturation of the renal excretory function.

A patent ductus arteriosus is frequently observed in preterm neonates and has possible consequences for renal and hepatic blood flow and hence for the renal and hepatic clearance of drugs.

Pharmacokinetic parameters vary considerably in infants. Half-life ranges from 5.4 to 10.0 hours, clearance from 0.50 to 1.71 ml/kg/min and volume distribution

from 0.4 to 0.7 l/kg. In adults the half-life of gentamicin is 2 to 3 hours, and the distribution volume is 0.3 l/kg. The higher total body water and fraction of extracellular water of infants compared to adults, results in a higher distribution volume with reported values of 0.5 to 0.7 l/kg in premature infants vs. 0.3 l/kg in adults. Gentamicin regimens must be individualized especially in prematures. Due to the accelerated maturation of renal tubules, there is an increased clearance of gentamicin with increasing gestational ages. Dosing must be adequately adjusted, if necessary.

In small for gestational age, the half-life is longer than in the appropriate for gestational age. In small for gestational age the intrauterine growth restriction may be associated with a decrease in nephron number and renal organ mass, altered tubular function, and impaired glomerular filtration. Therefore, in small for gestational age the clearance of gentamicin is lower ($p = 0.02$) than in appropriate for gestational age infants.

Hypothermic infants have impaired renal function compared to normothermic infants and their half-life is longer. The postnatal age is an important factor in determining the half-life and the clearance of gentamicin. At a postnatal age of 6 days half-life is longer than in infants with a postnatal age of 15 days.[33]

Some re-evaluations of the toxicology of gentamicin are in order here. A review of antibiotic prescriptions for 342 infants from 89 neonatal intense care unities revealed important points.[34] The 12 most frequently used antibiotics (gentamicin, penicillin G, ampicillin, vancomycin, amicacin, cefotaxime, ceftazidime, meropenem, amoxicillin, metronidazole, teicoplanin and flucloxacillin) covered 92% of prescriptions. Glycopeptide class, gestational age < 32 weeks, 5th minute Apgar score and geographical region were associated with deviations from the British National Formulary for Children dosage recommendation: doses of penicillin often exceeded recommendations; antibiotics with safety concerns either followed (gentamicin) or were dosed below (vancomycin) recommendations. Well-designed clinical trials with a limited number of antibiotics to define pharmacokinetics/pharmacodynamics, efficacy and safety in this population would be welcome. An efficient dissemination of the results should be undertaken to aid in the investigation of this lack of compliance.

Gentamicin is mainly dosed according to empirical guidelines, after therapeutic drug monitoring and subsequent dose adaptation. In view of the variety of neonatal guidelines available, a study was performed to evaluate target concentration attainment and proposed a new model-based dosing guideline for these drugs in neonates.[35] Demographic characteristics of 1,854 neonates (birth weight 390-5200 g, post-natal age 0-27 days) were retrospectively evaluated. Across the entire neonatal age and weight range, the Dutch National Formulary for children, the British National Formulary for Children, Neofax and the Red Book resulted in adequate peak but elevated trough concentrations. The new proposed dosing guidelines (4.5 mg/kg gentamicin) with a dosing interval based on birth weight and post-natal age leads to adequate peak concentrations with only 33%-38% of the trough concentrations. The proposed neonatal dosing guideline for gentamicin results in improved attainment of target concentrations and should be prospectively evaluated in clinical studies to evaluate the efficacy and safety of this treatment.

A study conducted on 113 Malaysian patients aged ≤ 28 days who received gentamicin treatment with dosing according to a regimen modified from an Australian-based pediatric guideline[36] found no significant difference between the percentage of term neonates vs. prematures who achieved adequate therapeutic concentrations. All but one of the subjects achieved the desired therapeutic trough concentration of < 2mg/l. Mean gentamicin peak concentration was 8.52 mg/l, trough concentrations 0.54 mg/l.

A prospective observational study was carried out on gentamicin concentrations achieved using a dosing table in neonates > 7 days old.[37] Neonates were given 5 mg/kg intravenously gentamicin; then a table using 22 hours post-first dose gentamicin concentrations was used to individualize dosing interval. Pre- and post-serum gentamicin concentrations were measured and used to calculate the true peak and trough concentrations achieved. Use of the table resulted in dosing intervals that provided appropriate peak (mean 9.8 ± 1.8 mg/l) and trough (mean 0.6 ± 0.3 mg/l) concentrations in all neonates, with all trough concentrations below 2 mg/l. The majority (87%) of peak concentrations were within the usual target range. Thus, the dosing table to individualize extended-interval gentamicin dosages resulted in appropriate peak and trough concentrations in all neonates studied.

Because glomerular filtration rate is responsible for the elimination of a large number of water-soluble drugs, a study was conducted based on an integrated analysis of gentamicin, tobramycin and vancomycin; this resulted in a semi-physiological function for glomerular filtration rate mediated clearance that can potentially be used to establish evidence based dosing regimens of renally excreted drugs in children.[38]

Recently, a covariate model characterizing development changes in clearance of amikacin in neonates has been developed using birth weight and postnatal age.[39] This model can be used to predict maturation in clearance of other drugs. Five different neonatal datasets were made available for netilmicin, vancomycin, tobramycin and gentamicin. The extensively validated covariate model for amikacin clearance was used to predict clearance of these drugs. In addition, independent reference models were developed based on a systemic covariate analysis. The descriptive and predictive properties of the models developed using the amikacin covariate model were

good. This study shows that pediatric covariate models may contain physiological information since information derived from one drug can be used to describe other drugs. This semi-physiological approach may be used to optimize sparse data analysis and to derive individualized dosing algorithms for drugs in children.

In conclusion, gentamicin is an important antibiotic against serious gram-negative aerobic bacteria. It inhibits bacterial protein synthesis and is the first choice antibiotic because of its reliable activity against most resistance gram-negative aerobes. The pharmacokinetic of gentamicin varies considerably in infants. In preterm infants, the half-life is longer and the clearance smaller than in full-term infants. Hypothermia, extracorporeal membrane oxygenation and the patent ductus arteriosus prolong the half-life of gentamicin. Postnatal age is an important determinant factor for the half-life of gentamicin; preterm infants have a longer half-life than full-term-infants. The trough concentration must be lower than 2 mg/l to avoid toxicity. The main toxical effects of gentamicin are ototoxicity and nephrotoxicity. More studies are required to provide a sound scientific basis for planning a dosage regimen with gentamicin in the neonate.

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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FARMACOLOGIA CLÍNICA DA GENTAMICINA EM NEONATOS: MODALIDADES DE USO, TOXICOLOGIA E FARMACOCINÉTICA

A gentamicina é antibiótico do grupo dos aminoglicosídeos. Destrói bactérias por inibição de síntese proteica e, em certa medida, por lise do envelope celular. A gentamicina é a droga de primeira escolha por causa de sua atividade confiável e em virtude de longa experiência com seu uso. Em combinação com antibióticos β-lactâmicos é recomendada para o tratamento de septicemia ou pneumonia e é ativa contra P. aeruginosa, Enterobacter, Klebsiella e Serratia. No entanto, a gentamicina é ototóxica e nefrotóxica. A variante genética mitocondrial humana m.1555A > G é tida como importante causa de disfunção auditiva hereditária não-sindrômica e pode causar perda permanente da audição. Até mesmo procedimentos terapêuticos de gentamicina de curta duração em recém-nascidos sadios podem levar a anormalidades da função auditiva. É ativa contra algumas espécies de bactérias apenas em concentrações de pico (> 10 mg/l) que são suficientemente altas para produzirem efeitos tóxicos. A gentamicina deve cair a concentrações mínimas menores que 2 mg/l para evitar efeitos tóxicos. Para produzir efeitos terapêuticos, as concentrações plasmáticas máximas de gentamicina deve variar de 4 a 10 mg/l. Os parâmetros farmacocinéticos variam consideravelmente em lactentes. A meia-vida varia entre 5,4-10,0 horas, o "clearance" varia entre 0,50 e 1,71 ml/h/kg e volume de distribuição de 0,4-0,7 l/kg. Em prematuros a meia-vida é mais longa do que a de crianças nascidas a termo. Por esses motivos, sempre que lactentes são tratadas durante 48 horas ou mais, monitorizar as concentrações séricas de gentamicina é essencial.

PALAVRAS-CHAVE: gentamicina, recém-nascido, nefrotoxicidade, ototoxicidade, farmacocinética, a toxicidade.

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