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Clinical pharmacokinetics in optimal gentamicin dosing regimen in neonates

Research Article

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Abstract: Gentamicin is readily used for suspected or proven sepsis in neonates, yet it shows considerable inter-individual pharmacokinetic variability, which limits achievements of therapeutic levels. Hence, the aim of this study was to compare peak and trough gentamicin concentrations according to dosing regimen, to evaluate pharmacokinetic parameters, and to consider adjustments of dosing regimen. Babies with infection were treated with 1 h infusion, and daily dose of 5 or 7.5 mg/kg depending on the age. Patients were randomized into two groups: I - dosing interval 12 h (n=8), II – 24 h (n=11). Two steady-state blood samples were obtained. Pharmacokinetic parameters were calculated using one-compartment model. The results showed a difference ($p<0.05$) in peak gentamicin concentrations between the groups, and tendency of lower trough levels in the group II. Calculated pharmacokinetic parameters included the volume of distribution (Vd) 0.52±0.47 l/kg, clearance (CL) 0.055±0.036 l/hkg and a half-life ($t_{1/2}$) of 6.89±3.21 h. Based on the method for dosing regimen adjustments, there was a need to extend dosing interval to 36 h in 6 patients.

Keywords: *Neonates • Gentamicin • Dosing regimen • Therapy individualization*

1. Introduction

Aminoglycosides, particularly gentamicin, are used in combination with β-lactam antibiotics for the treatment of presumed or proven sepsis in neonates. According to the national and international clinical guidelines, gentamicin may be administered via multiple (traditional) or once-daily (extended, prolonged interval) dosing regimen [1]. Gentamicin is given by repeated slow intravenous infusion for 0.5 or 1 h. Multiple daily dosing regimen involves administration of 2.5 mg/kg every 24 h in neonates <29 weeks of gestation, every 18 h if gestational age is between 29 and 35 weeks or every 12 h for neonates >35 weeks of gestation. Once-daily dosing regimen involves gentamicin administration of 4-5 mg/kg every 36 h for patients at <32 weeks of gestation and 4-5 mg/kg every 24 h for >32 weeks of gestation [1].

Exhibition of the post antibiotic effect at drug levels below the minimum inhibitory concentration (MIC), lower accumulation in the renal tubule and in the inner ear, avoidance of the development of bacterial resistance, and finally the pharmacoeconomic justification are all reasonable grounds to opt for once-daily dosing [2,3]. Results of some studies indicate that the administration of gentamicin once daily causes minor discrepancies in minimal (C_{trough}) and/or maximal (C_{peak}) concentrations from the desired therapeutic range. Based on the results of a number of studies, the use of gentamicin by once-daily regimen in neonates was as effective and safe as

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traditional dosing [4,5], whereas Croes et al. showed restricted nephro- and cochleo-toxicity with preserved efficacy upon administration of aminoglycosides once daily [6].

Neonates experience significant and dynamic changes in physiological processes that affect the pharmacokinetic characteristics of gentamicin. Compared with the adults, reduced content of fat and muscle tissues, increased percentage of body fluid (70-75% of total body weight) and an increased percentage of extracellular fluid (40% of total body weight) was observed [7,8]. Due to hydrophilic characteristics, gentamicin's volume of distribution (Vd) per kilogram of body weight is higher (some studies confirmed a two-fold increase) in the neonates compared with adults. The average values of gentamicin Vd in population of neonates are ranging from 0.45 to 0.75 l/kg. Being that gentamicin is mainly eliminated by kidney filtration, the glomerular filtration rate (physiological parameter of renal function) has an essential impact on the values of the gentamicin elimination parameters. In neonates, between 28 and 40 weeks of gestation, glomerular filtration rate is 30-50% of the value in adults, expressed as a function of body weight [7]. Renal function matures slowly, and depends on gestational and postnatal age. Thus, at birth the average blood flow through the kidneys is about 12 ml/min and increases up to 140 ml/min in the first two years of life [9]. Therefore, clearance (CL) of gentamicin is almost entirely dependent on glomerular filtration rate, and its values are from 0.53 to 1.72 ml/min/kg. Elimination half-life ($t_{1/2}$) is longer than in adults with values of 3-11 h [7]. Thus, large inter-individual variability in the gentamicin pharmacokinetics exists as a consequence of gestational age, postnatal age, weight, disease characteristics, and co-therapy. These factors directly affect the drug concentration in the blood. Thus, the value of C_{peak} is primarily dependent on Vd, whereas C_{trough} is primarily influenced by the CL and $t_{1/2}$. Therefore, there is a need in the clinical practice to optimize the gentamicin-dosing regimen. Being that gentamicin exhibits concentration-dependent efficacy and toxicity, therapeutic drug monitoring (TDM) is thus a recognized approach to individualize dosing regimen [3,10,11]. The recommended values for target therapeutic concentration depend upon the dosing regimen. Thus, the therapeutic gentamicin C_{peak} should be <10 mg/l if the drug is given every 12 h, or between 15 and 25 mg/l if the dosing interval is every 24 h. The target C_{trough} of gentamicin is <2 mg/l for drug administration at every 12 h or <1 mg/l for once daily administration [11].

The aim of this study was to compare C_{peak} and C_{trough} of gentamicin following a multiple and once daily dosing regimens in neonates with ≥37 weeks of gestation, in order to assess the gentamicin pharmacokinetic parameters and to adjust the dosing regimen.

2. Material and methods

2.1. Patients and therapy

This clinical study was performed in the Pediatric Intensive Care Unit and the Neonatal Unit at Pediatric Clinic, Institute for Health Care of Mother and Child "Dr Vukan Čupić" in Belgrade, Serbia, in the period between 1st September 2009 and 31st January 2010. The Ethics Committee of the Institute has approved the protocol of the study, and patients' parents were informed about the purpose and protocol of the study. Written consent was obtained before the enrolment.

Previously, diagnosis of sepsis (proven, probable, possible, nosocomial) was made according with the recommendations by the International Sepsis Definitions Conference, before initiation of the therapy. The study included up to 30 days old neonates with ≥37 weeks of gestation, where gentamicin therapy was indicated in combination with ampicillin or with third generation cephalosporin antibiotics, due to presumed or proven bacterial infection. Exclusion criteria comprised: birth before 37 weeks of gestation, presence of renal insufficiency and pre-given antimicrobial therapy.

Data of gestational age, body weight and body length at birth were obtained including gender, age and weight at the time of admission and Apgar score at 1st and 5th minute. In addition, data of maternal age, illnesses during pregnancy, status during labor, as well as treatment were collected in order to identify potential risk factors for the infection. Complete blood tests, C-reactive protein, urea, creatinine, β_2-microglobulin, serum electrolytes and bilirubin levels (where indicated), as well as urine analysis were performed in all neonates at admission. Cardiac function, respiratory rate/minute, blood pressure and oxygen saturation levels were monitored. Auditory function was also assessed with transient evoked otoacoustic emission (TEOAE) method, during first 3 days, and between 7th and 10th day of treatment.

Gentamicin was administered as 1 h intravenous infusion in 5% glucose solution. Patients were randomly allocated into one of two groups depending on the dosing regimen: 8 patients received the drug every 12 h (group I) and 11 patients every 24 h (group II). Patients aged 1-7 days received 5 mg/kg, whereas patients of 8 days and older received 7.5 mg/kg per day. Two steady-state blood samples (volume of 0.5-1 ml) were obtained from each patient: 1 h after the infusion, and the second immediately before the next dose.

2.2. Bioanalytical, pharmacokinetic and statistic analysis

Gentamicin concentrations were measured using a validated turbidimetric immunoassay (Thermo Scientific, UniCel® DxC Synchron® Systems, Beckman Coulter Inc., USA).

Based on these data, pharmacokinetic parameters for each patient were calculated, applying one-compartment linear model based on Sawchuk and Zaske method [12]. Elimination rate constant (β), $t_{1/2}$ and Vd were calculated using the following equations:

$$C_{trough} = C_{peak} \cdot e^{-\beta \cdot (\tau - t_i)}$$

$$C_{peak} = \frac{R \cdot \left(1 - e^{-\beta \cdot t_i}\right)}{\beta \cdot Vd \cdot \left(1 - e^{-\beta \cdot \tau}\right)}$$

where τ is the dosing interval, t_i is the infusion time, R is the rate of drug infusion calculated from the ratio of given dose and infusion time. CL was calculated by multiplying estimated values of Vd and β.

In order to assess the need for adjustments of dosing regimen, the concept of linear pharmacokinetics, recommended gentamicin therapeutic range and calculated individual values of pharmacokinetic parameters were used.

For descriptive and statistical analysis PASW Statistics® (ver. 18.0) was applied. Data suitability for specific test was verified. Therefore, use of Student's t- or Mann-Whitney U-test were considered to compare the differences in average gentamicin levels or pharmacokinetic parameter values between the groups, with level of statistical significance of $p<0.05$.

3. Results

Based on the inclusion/exclusion criteria, total of 19 neonates were enrolled in the study (Table 1). There was not a statistically significant difference in the patients' characteristics between the groups.

In group I, C_{peak} ranged from 5.70 to 9.22 mg/l, while in group II we observed levels from 4.84 to 24.62 mg/l. Nonparametric test was employed and statistical difference in the median C_{peak} values between groups was observed (Figure 1). C_{trough} values in group I ranged from 0.01 to 2.95 mg/l, while in group II they were between 0.75 and 2.60 mg/l. Statistical analysis showed that there is not a statistical difference in C_{trough} values between groups (Figure 1). The results indicate that C_{peak} above 10 mg/l was not reached in any of the patients in the group I, while in the same group C_{trough} was higher than 2 mg/l in 4 neonates. Furthermore, in group II, none

Table 1. Demographic characteristics of neonatal patients

CHARACTERISTIC	Gentamicin Dosing Regimen	
	group I (every 12 h) (n=8)	group II (every 24 h) (n=11)
Males	5 (62.50%)	5 (45.45%)
Age 1-7 [days]	6 (75%)	6 (54.54%)
Body weight [kg]	3.13 ± 0.35	3.32 ± 0.31
Body length [cm]	49.88 ± 3.04	50.45 ± 1.81
Apgar score at 1st minute	8 ± 1	8 ± 1
Apgar score at 5th minute	9 ± 1	9 ± 1
Serum creatinine levels on 1st day of therapy [μmol/l]	75.13 ± 19.76	60.27 ± 25.22
Serum creatinine levels on 3rd day of therapy [μmol/l]	44.88 ± 9.17	45.18 ± 12.12
Serum creatinine levels on 7th day of therapy [μmol/l]	43.75 ± 9.24	39.18 ± 7.52

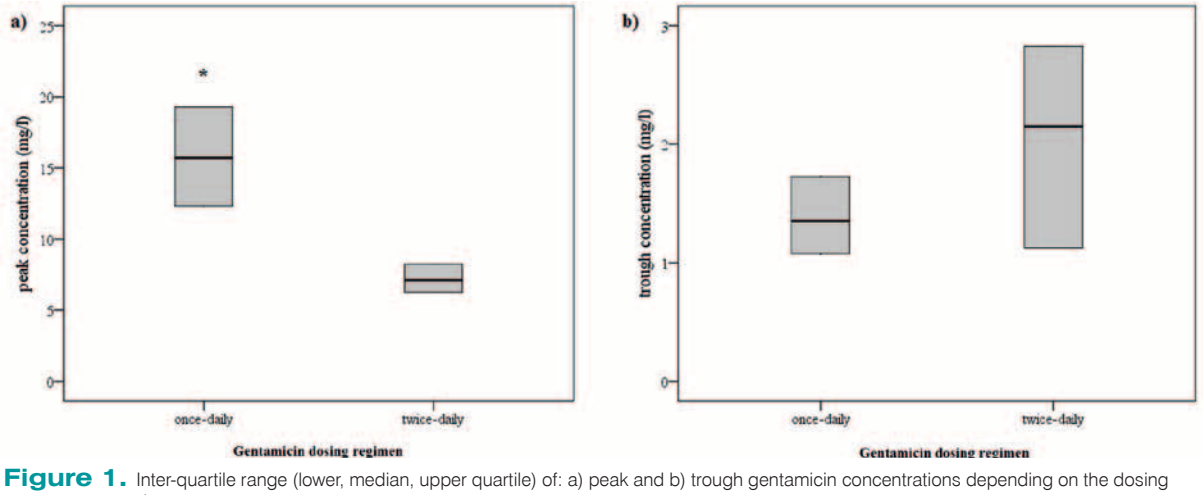

Figure 1. Inter-quartile range (lower, median, upper quartile) of: a) peak and b) trough gentamicin concentrations depending on the dosing regimen.

of the patients reached gentamicin levels higher than 25 mg/l, but in 5 patients C_{peak} was less than 15 mg/l, whereas in 8 patients C_{trough} was greater than 1 mg/l.

Individual values of pharmacokinetic parameters (CL, Vd and $t_{1/2}$) were calculated from the measured gentamicin concentrations. Table 2 shows the results for the full population of patients included in the study, and statistical difference between groups was not observed.

In order to assess the need for adjustments of dosing regimen, individual pharmacokinetic parameters and recommended therapeutic ranges of gentamicin were used. In the studied population, the extended dosing interval from 24 h to 36 h was needed in 6 patients undergoing once daily dosing regimen.

The difference was not observed in efficacy and toxicity between groups at the beginning and at the end of the treatment. In this study, creatinine levels and auditory function did not show marked change by the end of the therapy. All the patients were cured by the end of the treatment.

4. Discussion

The results of this study suggest that the use of gentamicin every 24 h in neonates ≥37 weeks of gestation has produced significantly higher peak concentrations, and there was a tendency for lower trough concentrations compared with twice daily regimen (Figure 1). This is in agreement with previously published data [4,13,14]. Lower C_{peak} could potentially impair the efficacy, due to failure in achieving desired ratio of the C_{peak} and minimum inhibitory concentration (MIC). Routine monitoring of the C_{peak} is not indicated when gentamicin is administered once daily, as it is expected to reach levels above those when given twice daily. According to the references, therapeutic gentamicin concentration C_{peak} is ranging from 15-25 mg/l, but it often exceeds 25 mg/l, which is not associated with adverse effects on clinical outcome [1,15]. However, concentrations below 15 mg/l could be linked with the potential inefficiency due to C_{peak}:MIC ratio <8:1 [3,11]. To confirm this hypothesis, information about the local sensitivity of isolated microorganisms would be valuable. In this study, in 5 patients C_{peak} were below 15 mg/l, which is probably due to the high Vd of gentamicin, possibly as a result of higher hydration via parenteral infusion.

In this study patients on once daily dosing (group I) had lower C_{trough} compared with group II. These levels were slightly higher than recommended range outlined above. The results of Cars and Odenholt suggest that gentamicin C_{trough} may be less than 0.3xMIC when previously high concentration was observed [16]. Therefore, in once daily regimen C_{trough} may approximate zero at the end of the dosing interval. Our results indicate the need to consider adjustments of the dosing regimen in individual patients. Accordingly, in the studied neonates, extension of the dosage interval from 24 h to 36 h may be considered. As previously elucidated, extension of the dosing interval is not expected to negatively affect drug's efficacy.

The calculated values of the pharmacokinetic parameters (CL, Vd, $t_{1/2}$) for each of the patients were assessed, and they are comparable with the results of previous studies [7,17-19]. Statistical difference in pharmacokinetic parameters was not detected between groups, confirming linear pharmacokinetics of gentamicin. However, wide inter-individual variability was observed. In the study by Mannan et al, difference in the renal function between pre- and full-term neonates was explained by gestational age [9], while Nielsen et al. showed that bodyweight, and both gestational and postnatal age were found to be main factors contributing to variability in gentamicin CL in neonates [15]. Furthermore, Knight et al, revealed significant difference between the mean trough concentrations assessed on day 2 versus days 3 or 4 [20]. Due to small sample size, multiple regression analysis could not be performed in our study in order to investigate the impact of gestational and postnatal age or bodyweight, on gentamicin pharmacokinetics.

In this study a rather small number of patients was included. Additionally, information regarding the local sensitivity of isolated microorganisms is necessary, and would be useful for an in-debth analysis. However, clinical studies including neonatal patients are always a great benefit to the scientific community and clinical practice due to wide spread use of genatmicin in the neonatal population.

Table 2. Gentamicin concentrations and pharmacokinetic parameters

PARAMETERS		mean value ± standard deviation
C_{peak} [mg/l]	group I - on 12 h	7.27 ± 1.27
	group II – on 24 h	15.53 ± 5.29
C_{trough} [mg/l]	group I - on 12 h	1.90 ± 1.08
	group II – on 24 h	1.47 ± 0.58
Vd [l/kg]		0.52 ± 0.47
CL [l/h/kg]		0.055 ± 0.036
β[h^{-1}]		0.1339 ± 0.1144
$t_{1/2}$ [h]		6.89 ± 3.21

C_{peak} peak concentration; C_{trough} trough concentration; Vd volume of distribution; CL clearance; β elimination rate constant; $t_{1/2}$ elimination half-life.

The results of this study indicate that significantly higher peak and a tendency of lower trough gentamicin concentrations were achieved after once daily regimen comparing with twice daily dosing. Furthermore, estimated pharmacokinetic parameters show considerable inter-individual variability, and highlight the need for routine therapeutic drug monitoring in order to individually optimize the gentamicin dosing regimen.

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Conflict of interest statement

Authors state no conflict of interest.

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