

Rationality of Administered Gentamicin Dose in Cerebral Coma Patients Treated in an Intensive Care Unit

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Abstract. Gentamicin is still widely used in the treatment of patients in an intensive care unit (ICU). The efficacy of aminoglycosides correlates with the peak serum concentration (C_{max}), and the toxicity with the minimum serum concentration (C_{min}). The aim of this study was to determine C_{max} and C_{min} in serum of cerebral coma ICU patients when a dosage of gentamicin of 5 mg/kg body weight was administered once daily; to evaluate the rationality of mentioned dose; and to identify factors associated with these concentrations.

Material and Methods. A total of 24 ICU patients suffering from cerebral coma were included into this analysis. A dosage of gentamicin of 5 mg/kg body weight was administered once a day. Gentamicin concentrations were tested twice after the first dose infusion (immediately and 5 hours after 1-hour infusion). C_{max} , C_{min} , volume of distribution (V_d), and elimination half-life ($T_{1/2}$) were obtained.

Results. The mean C_{max} was 17.96 (SD, 4.31) $\mu\text{g/mL}$ (range, 10.30–27.87 $\mu\text{g/mL}$). The desirable C_{max} ($\geq 20 \mu\text{g/mL}$) was reached only in 6 patients (25%). C_{min} was calculated using a special pharmacokinetic program “Kinetica.” C_{min} of 0.5 $\mu\text{g/mL}$ was not exceeded in any patient. A correlative analysis indicated a significant inverse direct correlation between C_{max} and V_d and between C_{max} and treatment duration in the ICU. An inverse correlation was observed between C_{min} and $T_{1/2}$, evaluation of coma according to the Glasgow coma scale, and creatinine clearance.

Conclusions. A dosage of 5 mg/kg body weight once a day was not sufficient in cerebral coma ICU patients. This dose was not associated with the nephrotoxic effect of gentamicin (additional risk factors were absent). It is recommended to obtain gentamicin concentration at two time points following administration of the first dose (e.g., immediately after 1-hour infusion and 5 hours later), and using a special pharmacokinetic software, to calculate a necessary dose and interval of administration.

Introduction

Aminoglycosides, including gentamicin, are still widely used for the treatment of patients in intensive care units (ICUs) despite the fact that a number of more advanced and possibly safer antibiotics have been introduced. This is caused by several factors: concentration-dependent bactericidal effect, concentration-dependent postantibiotic effect, rare occurrence of resistance, low price, synergisms with other beta-lactam antibiotics (1), and increased frequency of resistance of gram-negative pathogens to beta-lactam antibiotics and fluoroquinolones (2). Factors limiting the use of aminoglycosides are the following: narrow therapeutic index, relatively

frequent nephrotoxic effect (aminoglycosides are among the medicinal products most commonly causing a nephrotoxic effect), and irreversible ototoxic effect (3). The frequency of nephrotoxic effect caused by aminoglycosides used once a day reported in various sources varies from 0%–5% (4–6) to 14% (7). The inconsistency of data can be related to differences in the characteristics of patients (including the presence of other factors increasing the risk of nephrotoxicity), different dosing, and modification of doses regarding the pharmacokinetic parameters calculated.

In the past years, almost all hospitals in Lithuania introduced once-daily dosing of aminoglycosides.

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Various trials and meta-analyses have demonstrated that such a dosage regimen is simpler while the efficacy and toxicity are at least the same if compared to the conventional dosing of aminoglycosides, i.e., three times daily (patients with infectious endocarditis are an exception). Moreover, the prediction of pharmacokinetic parameters is more reliable with once-daily dosing (1, 4).

There is no common opinion regarding serum C_{max} of gentamicin. Literature data suggest various desirable serum C_{max}: 20 µg/mL (4), 8–11 µg/mL (8), and even 6 µg/mL (7). The most often recommended once-daily dose of gentamicin is 4–7 mg/kg body weight (9, 10). Selection of a dose depends on minimal inhibitory concentration (MIC) – it is recommended to exceed MIC 8–10 times (4, 9, 11, 12). According to Nicolou et al., MIC for *Pseudomonas aeruginosa* is 2 µg/mL; therefore, the desirable serum C_{max} is 16–20 µg/mL. Majority of the authors recommend a dose effective against bacteria with highest MIC for an ICU patient (4, 11, 12). In Lithuanian hospitals (e.g., Hospital of Lithuanian University of Health Sciences, Klaipėda University Hospital), the usual dose is up to 5 mg/kg body weight (13).

The accumulation of a medicinal product, i.e., the risk of toxic effect, is related to the serum C_{min} (i.e., concentration before the administration of the next dose). It is recommended not to exceed 1–1.5 µg/mL (4, 8, 9) or 2 µg/mL (7). Nicolau et al. recommends keeping serum C_{min} less than 0.5 µg/mL at least for 4 h (4).

The question if the rationality of usual dosing according to the nomograms is sufficiently rational in ICU patients is still open. Additionally, it is still not clear if pathophysiological changes related to coma do not influence pharmacokinetics of gentamicin. In this study, we aimed to determine what serum C_{max} and C_{min} of aminoglycosides (gentamicin) are achieved in cerebral coma patients in the ICUs administering a dose of 5 mg/kg body weight once a day. Additionally, we aimed to investigate if these concentrations are sufficiently rational in terms of efficacy and safety and to identify factors influencing these concentrations.

Material and Methods

Data on 24 patients treated at the Intensive Care Unit of Klaipėda University Hospital in 2008 were analyzed in this study. Gentamicin was administered and serum concentration was monitored in these patients. All the patients were in cerebral coma and suffered from pneumonia caused by gram-negative pathogens. Gentamicin at a dose of 5 mg/kg body weight was administered. If actual body weight exceeded ideal body weight by 20% or more, the specific formula was used to calculate dosing weight

Ideal body weight (IBW) (kg)

- IBW (males)=0.9 H–88
- IBW (females)=0.9 H–92

H, height (cm)

Weight used for determination of dose in case of overweight >20%

DW=IBW+0.4(ABW–IBW)

DW, dosing weight; ABW, actual body weight (kg)

Fig. 1. Determination of body weight used for dosing

(Fig. 1) (9). Two samples of venous blood were obtained following the infusion of the first gentamicin dose (immediately after the infusion, for detection of C_{max}, and 5 hours later, i.e., 1 and 6 hours following the beginning of the infusion). As it was expected that serum C_{min} will be extremely low and the possible bias high, serum C_{min} was not determined directly (it was calculated using a special program “Kinetica” for calculation of pharmacokinetic parameters). Gentamicin serum concentration was determined in the laboratory of Klaipėda Hospital using the immunoturbidimetry method (reagent “Quantia Gentamicin”). Pharmacokinetic parameters (C_{min}, V_d, and T_{1/2}) were calculated using concentrations measured from the samples obtained following infusion of the first gentamicin dose and 5 hours later with the help of a specific program for calculation of pharmacokinetic parameters “Kinetica” (Innapase Inc., the USA). Creatinine clearance was calculated using the Cockcroft-Gault method. Statistical analysis was performed using the SPSS 16 program. The associations between variables (associations of C_{max} and C_{min} with V_d, T_{1/2}, age, body weight, Glasgow coma scale [GCS] score, arterial blood pressure, creatinine clearance, treatment duration in an ICU, and central venous pressure) were estimated performing monofactorial analysis and using Spearman correlation. Differences in pharmacokinetic parameters between the groups of categorical parameters (associations between C_{max}, C_{min} and artificial ventilation) were determined using nonparametric Mann-Whitney criteria. The chosen level of significance was $\alpha=0.05$. Relation or difference was considered as statistically significant at $P<\alpha$.

Results

Demographic data (age, dosing weight, distribution according to sex), creatinine clearance, evaluation of coma according to the GCS, central venous pressure, and treatment duration in the ICU of 24 patients included in the analysis are presented in Table 1. Our study population represented general adult cerebral coma patients: they were body weight-matched, and a greater proportion of the

Table 1. Main Characteristics of the Patients (n=24)

Characteristic	Value
Age, years	53.58 (18.76) [17–77]
Dosing weight, kg	67.67 (12.30) [51–92]
Body weight, kg	69.96 (12.96) [51–94]
Males, n (%)	16 (67)
Females, n (%)	8 (33)
Creatinine clearance, mL/min	102.34 (44.96) [31.24–204.93]
Coma evaluation according to GCS, score	5.54 (2.93) [3–14]
Central venous pressure, cm	9.48 (2.21) [7–14]
Treatment duration in ICU, days	5.92 (3.12) [1–15]

Data are mean (SD) [range] unless otherwise indicated.
GCS, Glasgow coma scale.

patients were males. Renal dysfunction (creatinine clearance, <60 mL/min) was documented in 4 patients (17%). All patients were treated with concomitant medications, mainly electrolytes and infusions (n=24), beta-lactam antibiotics (n=12), and mannitol (n=8). Fifteen patients (62.5%) underwent head surgery. Artificial pulmonary ventilation was applied in 12 patients (50%).

Analysis of pharmacokinetic parameters was carried out. The main data are presented in Table 2. The mean serum C_{max} was 17.96 µg/mL (from 10.30 µg/mL to 27.87 µg/mL). The desirable serum C_{max} (≥20 µg/mL) was achieved in 6 patients. Serum C_{min} was not higher than 0.5 µg/mL in any patient. The mean V_d was 0.23 L/kg body weight,

and the mean T_{1/2} was 1.85 h.

Correlation analysis was carried out. A direct inverse correlation between serum C_{max} and V_d (Spearman correlation coefficient, $R_s = -0.851$, $P < 0.001$) (Fig. 2) and between serum C_{max} and treatment duration in the ICU ($R_s = -0.433$, $P = 0.035$) (Fig. 3) was found. An inverse correlation was found between serum C_{min} and T_{1/2} ($R_s = -0.997$, $P < 0.001$), evaluation of coma according to the GCS ($R_s = -0.587$, $P = 0.003$), and creatinine clearance ($R_s = -0.628$, $P = 0.001$).

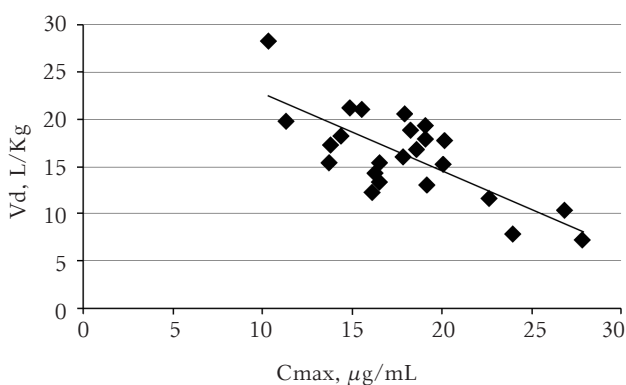
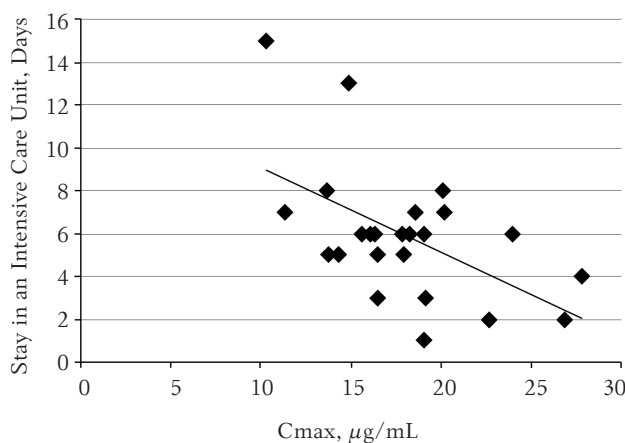
Discussion

Usually, an intravenous infusion of aminoglycosides is recommended, and the duration of infusion is 0.5 h or 1 h (9, 14). In some countries (e.g., Scandinavian countries), a rapid (bolus) infusion of aminoglycoside is used; however, this method of administration is not well studied, and almost all data about aminoglycosides found in the scientific literature have been gathered using aminoglycosides via infusion (1). Most of the trials indicate that toxic effects correlate with serum C_{min}, and efficacy correlates with serum C_{max} (9, 15–17); however, some authors have doubts regarding these considerations (7).

The findings of this study indicate that following the infusion of 5 mg/kg body weight, serum C_{max} of >20 µg/mL was achieved in 6 patients (25%), and the mean serum C_{max} was 17.96 µg/mL. Thus, a dosage of 5 mg/kg body weight is not sufficient in cerebral coma patients treated in the ICU. These patients

Table 2. Basic Pharmacokinetic Parameters (n=24)

Pharmacokinetic parameter	Mean	Standard deviation	Minimal value	Maximal value	Median
Peak serum concentration C _{max} , µg/mL	17.96	4.31	10.30	27.87	17.87
Volume of distribution V _d , L/kg body weight	0.23	0.06	0.14	0.38	0.22
Elimination half-life T _{1/2} , h	1.85	0.74	0.87	3.66	1.59

Fig. 2. Correlation between C_{max} and V_d (n=24, $P < 0.001$)Fig. 3. Correlation between C_{max} and duration of treatment in the ICU (n=24, $P = 0.035$)

should be treated with an infusion dose of 7 mg/kg body weight. These findings were confirmed by Buijk et al. (18); however, Rea et al. concluded that there was only a 20% and 40% probability that patients receiving 7 mg/kg of gentamicin and tobramycin, respectively, will achieve pharmacodynamic target over the range of MIC distributions (19).

This study showed a direct inverse correlation between serum C_{max} and V_d and treatment duration in an ICU, as it was expected. High variation in serum C_{max} (from 10.30 µg/mL to 27.87 µg/mL, i.e., more than 2.5 times) corresponds to the literature data regarding ICU patients (11, 20–22). Such a variation of 300% and variation of 300% in V_d and 400% in T_{1/2} indicate that pharmacokinetic parameters of cerebral coma patients are highly variable; therefore, dosing cannot be precisely predicted based only on nomograms.

Aminoglycosides, including gentamicin, are excreted via kidneys (≥90%) in an unchanged form, mainly via glomerular filtration, and the rate of elimination is directly proportional to creatinine clearance (9). The risk of nephrotoxic effect increases in case of prolonged duration treatment (7, 8, 23, 24), concomitant use of nephrotoxic agents (7, 25), and high (>0.5–2 µg/mL) serum C_{min} (7, 13, 23, 24).

The serum C_{min} and consequently the risk of toxic effect (especially nephrotoxic) may be reduced by either decreasing the dose or increasing the time intervals between infusions (7). Some of authors, such as Nicolau et al. and Hansen et al., recommend increasing the time intervals between administrations of medications; others like Prins et al. suggest decreasing a dose (1, 4, 7). The latter suggestion raises some doubts because an effective serum C_{max} may be not achieved in this case.

In this study, the serum C_{min}, calculated using a special program for calculation of pharmacokinetic parameters, was not higher than 0.5 µg/mL in any patient including patients with renal dysfunction; consequently, there is no risk of nephrotoxic effect caused by gentamicin, at least in patients with normal function and in absence of other risk factors, administering a dosage of 5 mg/kg body weight every 24 hours. There was a statistically significant

correlation between serum C_{min} and T_{1/2} and between C_{min} and creatinine clearance, and these findings correspond to the literature data.

As toxic effects correlate with serum C_{min}, efficacy correlates with serum C_{max}, and pharmacokinetic parameters vary widely in ICU patients, the monitoring of aminoglycoside serum concentrations followed by the dose correction is highly recommended (4, 26–29). Dosing corrected according to pharmacokinetic parameters helps to achieve the optimal serum concentration and decreases the risk of toxic effect. Moreover, the frequency of toxic effects may be decreased by the assessment of other risk factors, monitoring of pharmacokinetic parameters, and making necessary corrections of dosing and administration time intervals (4, 7, 8, 14, 29).

The following dosing scheme is proposed: the selected initial dose of gentamicin (e.g., 7 mg/kg body weight) is administered, and then two serum concentrations are obtained (C_{max}, i.e., immediately after 1 hour infusion, and then one more, e.g., 5 hours after infusion). Using one of the numerous programs for pharmacokinetic calculations (e.g., Siphar/Win [Simed], PKS [Abbott]), pharmacokinetic parameters (V_d and T_{1/2}) should be calculated and desirable serum C_{max} and C_{min} selected. The program will calculate the dose and interval of administration.

Conclusions

Taking into account serum C_{max}, it can be concluded that gentamicin administered at a dosage of 5 mg/kg body weight once daily was not sufficiently effective in cerebral coma patients treated in the intensive care unit. Gentamicin administered at a dosage of 5 mg/kg body weight once daily did not increase the risk of nephrotoxicity in the absence of other risk factors. Treatment duration in the intensive care unit is a risk factor for unsuccessful achievement of effective concentration: the longer is hospital stay in the intensive care unit, the higher is the risk that the administered dose will be insufficient.

Statement of Conflict of Interest

The authors state no conflict of interest.

Cerebrinė komą patyrusiems intensyviosios terapijos pacientams skiriamos gentamicino dozės racionalumo tyrimas

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Raktažodžiai: gentamicinas, farmakokinetika, dozavimas.

Santrauka. Gentamicinas vis dar plačiai vartojamas intensyviosios terapijos skyriaus (ITS) pacientams gydyti. Aminoglikozidų veiksmingumas koreliuoja su didžiausia koncentracija serume (C_{max}), toksinis poveikis – su mažiausia koncentracija serume (C_{min}).

Tyrimo tikslas. Apskaičiuoti, kokia C_{max} ir C_{min} būna ITS pacientų, patyrusių cerebrinę komą, serume, kai kas 24 val. skiriama 5 mg/kg kūno svorio gentamicino dozė, nustatyti, ar šios koncentracijos būna racionalios, panagrinėti, kokie veiksniai turi įtakos gentamicino koncentracijai serume.

Tirtųjų kontingentas ir tyrimo metodai. Į šią analizę įtraukti cerebrinę komą patyrę 24 ITS pacientai, kuriems kartą per parą buvo infuzuojama 5 mg/kg kūno svorio gentamicino dozė. Gentamicino koncentracija buvo tirta po pirmosios dozės suleidimo du kartus (iškart bei praėjus 5 val. po 1 val. trukmės infuzijos) ir pagal gautus duomenis nustatyti C_{max} , C_{min} , pasiskirstymo tūrį (V_d) bei pusinės eliminacijos laiką ($T_{1/2}$).

Rezultatai. C_{max} buvo 17,96 ($\pm 4,31$) $\mu\text{g/ml}$, ji varijavo nuo 10,30 $\mu\text{g/ml}$ iki 27,87 $\mu\text{g/ml}$. Pageidautina, t. y. veiksminga visų jautrių bakterijų atveju (20 $\mu\text{g/ml}$ arba didesnė) C_{max} pasiekta tik 6 (25 proc.) ligoniams. Pagal farmakokinetinę programą „Kinetica“ apskaičiuota C_{min} , kuri nė vienam ligoniui nebuvo didesnė nei 0,5 $\mu\text{g/ml}$. Atlikus koreliacinę analizę, nustatytas statistškai patikimas atvirkštinis tiesinis ryšys tarp C_{max} ir V_d bei gydymo ITS trukmės (dienomis). Atvirkštinė koreliacija nustatyta tarp C_{min} ir $T_{1/2}$, komos įvertinimo pagal GKS bei kreatinino klirensu.

Išvados. Kartą per parą vartojama 5 mg/kg kūno svorio gentamicino dozė nėra pakankamai veiksminga ITS pacientams, patyrusiems cerebrinę komą. Gentamicino nefrotoksinio poveikio pavojaus, vartojant 5 mg/kg kūno svorio dozę kas 24 val., nekyla (jei nėra papildomų rizikos veiksnių). Po pirmosios gentamicino dozės infuzijos rekomenduojama du kartus ištirti gentamicino koncentraciją serume (pvz., iškart bei praėjus 5 val. po infuzijos) ir, panaudojant farmakokinetinių skaičiavimų programą, apskaičiuoti reikiamą dozę bei vartojimo dažnumą.

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