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Is gentamicin administered to individual patients in optimal doses already at the beginning of therapy?

Original research article/Review

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Abstract ***Introduction*** A gentamicin dose, which the physicians select, frequently does not take any pharmacokinetic parameters into consideration.
Aim To analyse the results of therapeutic drug monitoring (TDM) of gentamicin for those patients who have not had the gentamicin dose adjusted at the beginning of therapy (first group) and for those patients who had the gentamicin dose adjusted at the beginning of therapy (second group).
Methods We acquired the basic data about patients from the requests for laboratory examination of levels of gentamicin. We measured all the gentamicin concentrations mentioned in this work using the FPIA method.
Results The monitored set included 379 hospitalized patients during a 4-year period. We divided the monitored set into 2 groups. First group was composed of patients without dose adjustment of gentamicin at the beginning of therapy, and the second group was composed of patients with dose adjustment of gentamicin by the clinical pharmacist at the beginning of therapy. In addition, the patients in each group were divided according to the body mass index (BMI). In the first group of patients, a low percentage of patients had both optimal levels (trough, peak levels). As for patients with BMI > 25 m^2/ kg, there were only 17 % such cases, and the patients with BMI ≤ 25 m^2/kg were only 18.8 %. In the second group, the patients had all trough and peak levels in optimal therapeutic range at obese patients, overweight patients and also at patients with normal weight ($p < 0.001$).
Conclusion Adjustment of dosage regimens immediately at the beginning of therapy will provide for administering sufficient doses of antibiotics at the beginning of therapy, which is a pre-condition for a successful anti-infective therapy. Therapeutic monitoring of levels allows for administration of sufficient dose of gentamicin without fear of any undesirable effects.

Keywords *Gentamicin – therapeutic drug monitoring – adjustment of dosage of gentamicin*

INTRODUCTION

Gentamicin has been used in clinical practice for more than 50 years due to its good bactericidal effect, which is dependent on its concentration, low resistance, synergy with beta-lactam antibiotics, and finally, also due to its low price (Martin et al., 2012). Nephrotoxicity and ototoxicity have discouraged physicians from frequently using gentamicin and other aminoglycosides in clinical practice. Current advances in proper administration have returned them again among the effective antibiotics against gram-negative bacteria that have a place in clinical practice (Durante-Mangoni et al., 2009). Gentamicin is used in combination with other antibiotics, mainly for the treatment of serious infections (Gómolka & Niemczyk, 2014). In Teaching Hospital Nitra, gentamicin is a frequently used antibiotic due to the abovementioned reasons. Most frequently, it is part of an anti-infective therapy at clinics and surgical departments. In the monitored set of 379 patients who had been administered gentamicin over the period of four years, the proportion of patients hospitalized at clinics and surgical departments was as high as 70.7%. In the recommendations of specialist infectious and surgical associations in North America, gentamicin is a part of combined antibiotic therapy, used in the treatment of

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intra-abdominal infections in children and adults (Solomkin et al., 2010). Patients in the monitored set were administered gentamicin in 92% in combination with other antibiotics. Another significant advantage of gentamicin treatment in the Teaching Hospital Nitra is a possibility of **therapeutic drug monitoring (TDM)** in the hospital pharmacokinetic laboratory and the follow-up interpretation of TDM results and proposal for dosage regimens by the clinical pharmacist.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Teaching Hospital Nitra.

METHODS

Prospective monitoring *included* all adult patients for whom the serum levels of gentamicin were measured (trough and peak levels) during the period from 1st August 2010 to 1st August 2014 in the Pharmacokinetic Laboratory of the Teaching Hospital Nitra.

Patients

All the patients were hospitalized at different clinics and departments of the Teaching Hospital Nitra. We acquired the basic data about patients from the requests for laboratory examination of levels of gentamicin, which were sent to the pharmacokinetic laboratory with samples of biological material.
Demographic and biometric data were collected by means of the mentioned requests: age, gender, actual weight (ABW), height, serum creatine level (SCr), and information on dosage regimen for gentamicin. We calculated the BMI (body mass index) according to the formula. The pharmacokinetic parameters: Cocrofta-Gaulta Creatinine Clearance ($CrCl_{CG}$), total clearance of gentamicin (total Cl), the total distribution volume of gentamicin (total Vd), elimination rate constant (ke), biological half-life ($t_{1/2}$), and ideal weight (IBW) were obtained using the pharmacokinetic program *(Abbottbase Pharmacokinetic Program)*.
In this work, the set of patients was divided into two groups: The first group consisted of the patients who did not have the gentamicin dosage regimen adjusted at the beginning of therapy; the second group consisted of the patients who had the gentamicin dosage regimen adjusted immediately at the beginning of therapy according to the current pharmacokinetic parameters.

Laboratory methods

We measured all gentamicin concentrations mentioned in this work using the FPIA method on the analyser AxSYM of company ABBOTT in the Pharmacokinetic Laboratory of the Teaching Hospital Nitra.

Statistical methods

Patient demographic and pharmacokinetic parameters were represented by simple arithmetic mean, standard deviation, or confidence intervals (CI).
Description characteristics were calculated for demographic parameters and dose size. When comparing two groups, a two-sample t-test was used. For the pairwise linear regression (analysis) by the parametric linear least squares method, significance by the linear ANOVA method was evaluated, and consequently, the significance of the contrast and slope of the linear model was independently tested. To determine the statistical significance of association between nominal or ordinal variables arranged in the contingency table, Fisher's exact test and Yates's corrected Chi-square test were used, respectively.

Aim of the study

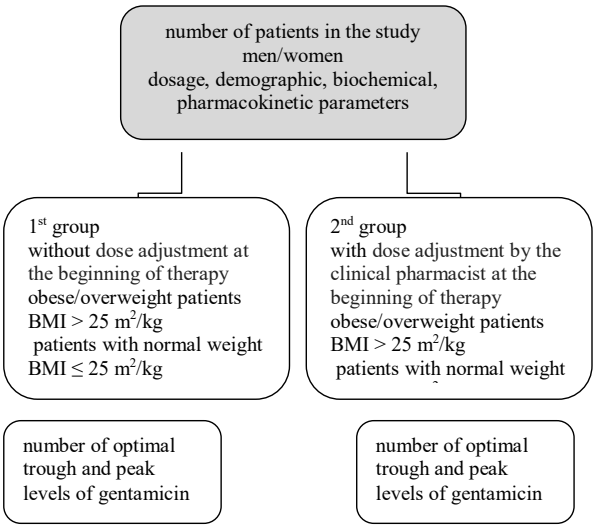
- To analyse the results of therapeutic monitoring of serum levels of gentamicin of patients who **have not had the gentamicin dose adjusted at the beginning of therapy**, according to the pharmacokinetic parameters
- To analyse the results of therapeutic monitoring of serum levels of gentamicin of patients who **had the gentamicin dose adjusted at the beginning of therapy**, according to the pharmacokinetic parameters
- Comparisons of results of determined levels of gentamicin at trough and peak levels of concentrations in both groups of patients regarding the pharmacokinetic parameters and dosage regimen for gentamicin

Design of the study

Design of the study is depicted in the following scheme, as shown in Figure 1.

RESULTS

Based on the inclusion criteria, the set included 379 patients, who had the trough and peak levels of gentamicin monitored. All the patients included in the prospective monitoring were hospitalized at the clinics and departments of the Teaching Hospital Nitra; in the total set of 379 pateints, there were 299 men (78.9%) and 80 women (21.1%). 268 patients (n = 379; 70.7%) were hospitalized at surgical clinics and departments, and 111 patients (n = 379; 29.3%) were hospitalized at clinics and departments of conservative disciplines. The highest number of patients in both groups represented the patients at the Surgery Clinic, the Clinic of Accident Surgery and the Orthopaedics and at the Infectious Disease Clinic. Patients were divided into two groups. The first group consisted of 204 patients, who did not have the gentamicin dosage regimen adjusted at the beginning of therapy; the second group consisted of 175 patients, who had the gentamicin dose



BMI – body mass index

Figure 1. Design of the study

regimen adjusted by the clinical pharmacist immediately at the beginning of therapy according to the current pharmacokinetic parameters. The total number and ratio (%) of patients hospitalized at individual clinics/departments in the first and second group is stated in Table 1. Demographic data and pharmacokinetic parameters of both groups are given in Table 2 and 3.

Difference in ratio of men in the first group (n = 204; 79.4%) and the second group (n = 175; 78.4%) was not significant. Age average in the second group of patients with dose adjustment at the beginning of therapy was significantly lower ($p < 0.05$); the other demographic data and serum creatine were not significantly different. Pharmacokinetic parameters that prove better elimination of gentamicin were significantly better ($p < 0.05$) in the second group of patients. For better comparison and assessment of dosage regimens and consequently determined levels, we further divided the first and second group of patients according to the BMI (body mass index) into two sub-groups. One sub-group included obese patients and overweight patients with BMI > 25 kg/

Table 1. The total number and ratio (%) of patients hospitalized at individual clinics/departments in first and second group.

Clinic/department	**First group n = 204 (%)** without dose adjustment of gentamicin at the beginning of therapy	**Second group n = 175 (%)** with dose adjustment of gentamicin at the beginning of therapy	Total **n = 379 (%)**
Clinic of Surgery	**84 (41.2)**	**99 (56.6)**	**183 (48.3)**
Clinic of Gynaecology and Obstetrics	1 (0.5)	4 (2.3)	5 (1.3)
Infectious Disease Clinic	**21 (10.3)**	**17 (9.7)**	**38 (10.0)**
Internal Clinic	13 (6.4)	5 (2.8)	18 (4.7)
Cardiology Clinic	22 (10.7)	4 (2.3)	26 (6.9)
Anaesthesiology and Intensive Care Clinic	10 (4.9)	4 (2.3)	14 (3.7)
Department of Dermatology	1 (0.5)	0	1 (0.3)
Clinic of Accident Surgery and Orthopaedics	**24 (11.7)**	**32 (18.2)**	**56 (14.8)**
Clinic of Neurosurgery	0	1 (0.6)	1 (0.3)
Clinic of Neurology	5 (2.5)	1 (0.6)	6 (1.6)
Department of Vascular Surgery	7 (3.4)	3 (1.7)	10 (2.6)
Department of Plastic Surgery	2 (1.0)	0	2 (0.5)
Department of Oncology	4 (2.0)	4 (2.3)	8 (2.1)
Department of ORL	4 (2.0)	1 (0.6)	5 (1.3)
Department of Urology	6 (2.9)	0	6 (1.6)

Table 2. Demographic parameters and biochemical parameters in first and second group.

Demographic parameters	**First group n = 204** without dose adjustment of gentamicin at the beginning of therapy	**Second group n = 175** with dose adjustment of gentamicin at the beginning of therapy	**p**
Age [year]	57 ± 17 (55–60)	53 ± 17 (51–55)	**p < 0.05**
Sex (men/women)	160/44	139/36	
Actual body weight (ABW) [kg]	84 ± 22 (81–88)	87 ± 19 (84–89)	0.238
Ideal body weight (IBW) [kg]	65 ± 8 (64–66)	65 ± 11 (64–67)	0.754
Height [cm]	174 ± 9 (173–175)	174 ± 9 (173–175)	0.273
Biochemical parameter			
Creatinine concentration [μmol/l]	84.2 ± 33.3 (79.6–88.7)	83.6 ± 20.6 (80.5–86.6)	0.823

Mean ± standard deviation (SD), (95% confidence interval), Two-choice t-test

Table 3. Pharmacokinetic parameters of gentamicin in first and second group.

Pharmacokinetic parameters	**First group n = 204** without dose adjustment of gentamicin at the beginning of therapy	**Second group n = 175** with dose adjustment of gentamicin at the beginning of therapy	**p**
Creatinine clearance (ABW) [ml/min/1.73 m^2]	94.0 ± 40.5 (88.4–99.6)	93.1 ± 30.1 (88.6–97.3)	0.590
Creatinine clearance (IBW) [ml/min/1.73 m^2]	74.5 ± 35.7 (69.6–79.5)	72.7 ± 28.9 (68.4–77.0)	0.798
Total clearance [l/h]	4.5 ± 2.0 (4.2–4.8)	5.3 ± 2.1 (5.1–5.7)	**p < 0.05**
Total distribution volume V_d [l]	16.2 ± 2.1 (15.9–16.5)	16.5 ± 2.0 (16.2–16.8)	0.210
Elimination rate constant k_e [h^{-1}]	0.288 ± 0.165 (0.265–0.310)	0.325 ± 0.123 (0.307–0.344)	**p < 0.05**
Half-life $t_{½}$ [h]	3.01 ± 1.42 (2.81–3.20)	2.45 ± 1.04 (2.30–2.61)	**p < 0.05**

Mean ± standard deviation (SD), (95% confidence interval), Two-choice t-test

m^2. The other sub-group included patients with normal body weight with BM I ≤ 25 kg/m^2.

In the first group of patients without dose adjustment of gentamicin at the beginning of therapy, gentamicin was administered in the dosage regimen once daily only for 9 (n = 135; 6.7%) obese and overweight patients and for 6 patients with normal body weight (n = 69; 8.6%). In the second group of patients with dose adjustment by the clinical pharmacist at the beginning of therapy, the dosage regimen once daily was preferred for 125 obese and overweight patients (n = 128; 97.6%) and for all 47 patients with normal body weight (n = 47; 100%). Gentamicin was the most frequently administered in regimen 320 mg every 24 hours to both groups of patients and 360 mg every each 24 hours in the group of obese and overweight patients. Comparison of dosage regimens in individual groups of patients divided according to BMI is depicted in Figure 2 and Figure 3.

Daily doses of gentamicin considering the pharmacokinetic parameters, which were calculated for the patients of second group with BMI > 25 kg/m^2 and with BMI ≤ 25 kg/m^2 at the beginning of therapy, were significantly higher ($p < 0.001$) in contrast to the first group of patients. Patients of first group without dose adjustment of gentamicin considering the pharmacokinetic parameters were administered lower doses at the beginning of the therapy and most patients were under dosed (Table 4).

In the second group of patients with dose adjustment of gentamicin at the beginning of therapy, all trough and peak

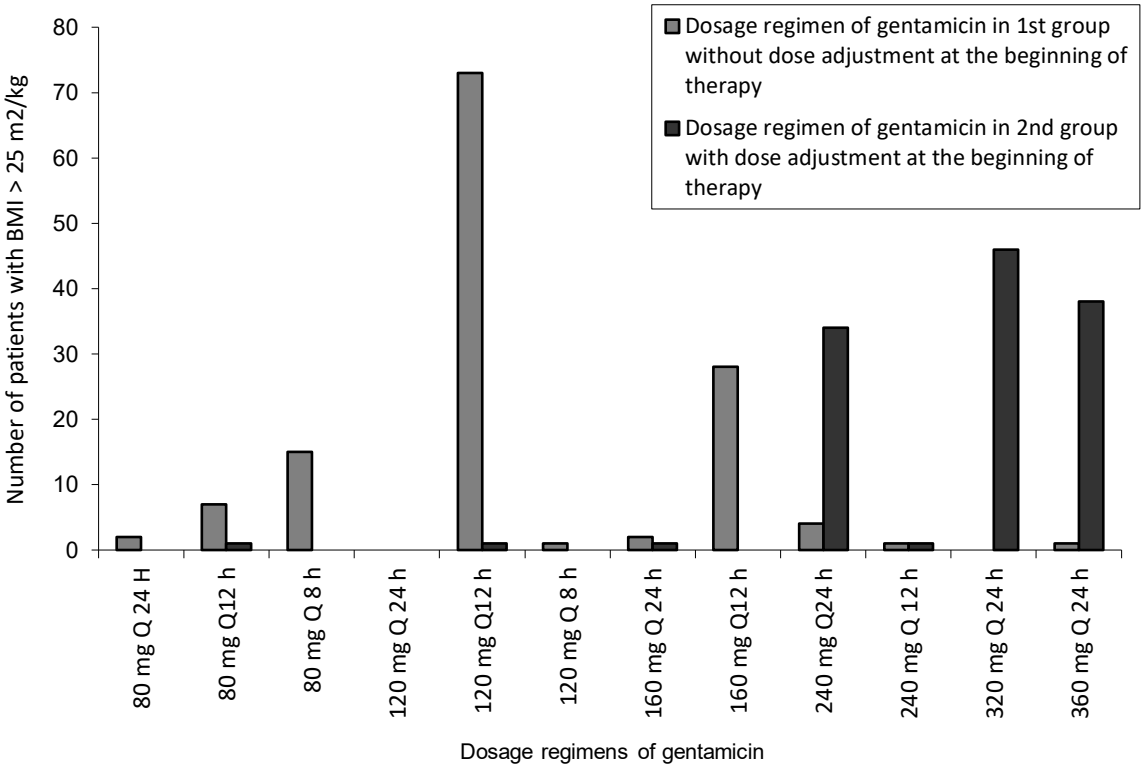


Figure 2. Stratification of patients with BMI > 25 m²/kg according to daily doses of gentamicin in first and second group.

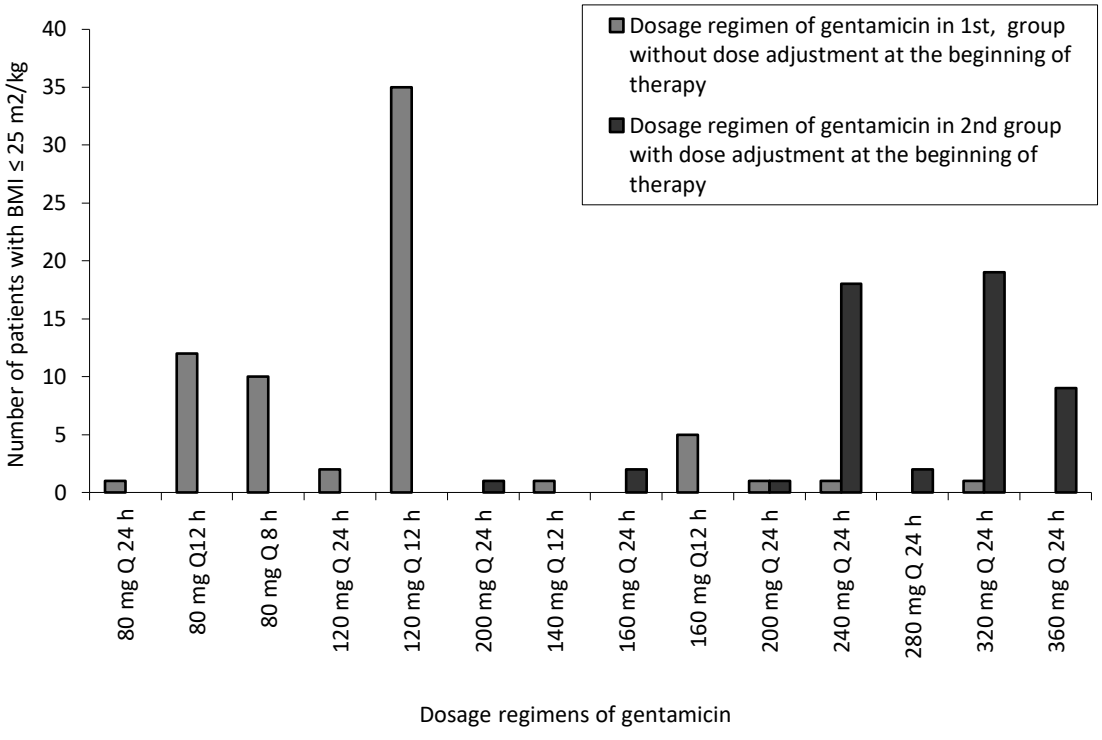


Figure 3. Stratification of patients with BMI ≤ 25 m²/kg according to daily doses of gentamicin in first and second group.

Table 4. Comparison of daily doses of gentamicin in first and second group.

Daily doses of gentamicin [mg/kg/day]	**First group n = 204** without dose adjustment of gentamicin at the beginning of therapy	**Second group n = 175** with dose adjustment of gentamicin at the beginning of therapy	**p**
Patients with BMI > 25 m^2/kg	2.7 ± 0.6 (2.6–2.8) n = 135	3.3 ± 0.6 (3.1–3.4) n = 128	**p < 0.001**
Patients with BMI > 25 m^2/kg	3.5 ± 0,9 (3.3–3.8) n = 69	4.3 ± 0.8 (4.1–4.6) n = 47	**p < 0.001**

Mean ± standard deviation (SD), (95% confidence interval) ANOVA test

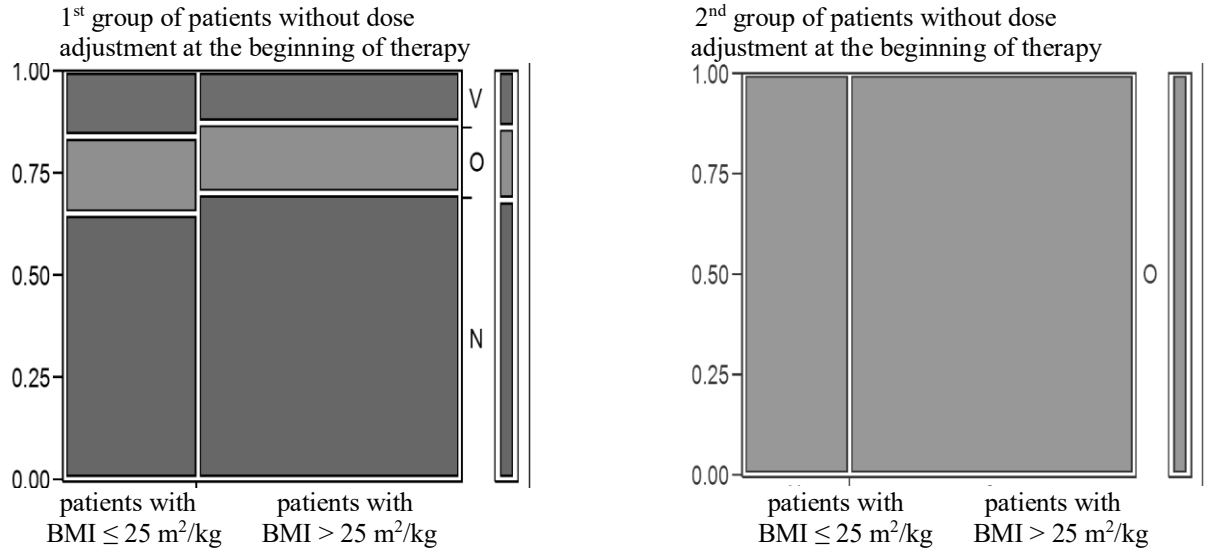


Figure 4. Contingency analysis. Number of patients with optimal levels of gentamicin in first and second group.

levels were in optimal therapeutic range for patients with BMI > 25 m^2/kg and with BMI ≤ 25 m^2/kg. In contrast with the first group of patients without dose adjustment at the beginning of therapy, in which only low percentage of patients had both optimal levels. For patients with BMI > 25 m^2/kg, it was only 17% and patients with BMI ≤ 25 m^2/kg only 18.8%. Ratio of optimal levels in both groups is depicted in the contingency analysis (Figure 4).

Differences between both groups in average trough and peak levels were highly statistically significant. Patients with dose adjustment at the beginning of therapy reached significantly lower trough levels and higher peak levels ($p < 0.001$), which is desirable for efficiency and safety of treatment by gentamicin (Table 5).

Adjustment of gentamicin dose for an individual patient at the beginning of the therapy allowed to reach the target values of gentamicin concentrations better and faster.

Success of gentamicin dose adjustment by the clinical pharmacist at the beginning of the therapy with regard to reaching efficient levels is statistically significant. If a correct dosage regimen is selected, there is a high chance to reach optimal peak level, which is also confirmed by the result of statistical calculation: OR is 193.59 (95% CI 46.55–805.09).

DISCUSSION

For all the patients of the second group with dose adjustment by the clinical pharmacist at the beginning of the therapy at first **determination of levels,** trough and peak levels of gentamicin concentrations reached the desired optimal therapeutic range (100%) in contrast with the first group of patients without dose adjustment at the beginning of therapy, where only 17.7% patients reached the optimal values at both levels.

As early as in the work of Thomson et al. (1996), patients with dose adjustment of gentamicin at the beginning of therapy –

Table 5. Comparison of trough and peak levels of gentamicin in first and second group.

Optimal range	**First group n = 135** without dose adjustment of gentamicin at the beginning of therapy with BMI > 25 kg/m^2	**Second group n = 128** with dose adjustment of gentamicin at the beginning of therapy with BMI > 25 kg/m^2	**p**
Trough levels [mg/l] < 2 mg/l	0.96 ± 0,75 (0.83–1.1)	0.43 ± 0.26 (0.38–0.47)	**< 0.001**
Peak levels [mg/l] 5–10 mg/l, >10 mg/l - once daily dosage	4.55 ± 2.26 (4.17–4.94)	10.03 ± 2.94 (9.51–10.54)	**< 0.001**
	First group n = 69 without dose adjustment of gentamicin at the beginning of therapy with BMI ≤ 25 kg/m^2	**Second group n=47** with dose adjustment of gentamicin at the begining of therapy with BMI≤ 25 kg/m^2	**p**
Trough levels [mg/l] < 2 mg/l	1.08 ± 0.98 (0.84–1.32)	0.44 ± 0.31 (0.35–0.53)	**<0.001**
Peak levels [mg/l] 5–10 mg/l, >10 mg/l - once daily dosage	5.03 ± 2.30 (4.47–5.58)	11.30 ± 2.88 (10.46–12.13)	**<0.001**

Mean ± standard deviation (SD), (95 % confidence interval) ANOVA test

their levels reached in high percentage optimal therapeutic range. The Thomson's study compared a group of 50 patients who were administered gentamicin only in empirically selected dose and 50 patients who were administered gentamicin according to elaborated recommendations. In the group of patients whose dosage regimen of gentamicin reflected the recommendations, peak levels reached significantly higher values (7.2 ± 1.9 vs. 5.7 ± 1.8 mg/l) and 96% of them had optimal both levels. Only 59% of patients who were administered gentamicin in empirically selected dose had optimal both levels.

Cox et al. (2011) compared trough levels of aminoglycoside antibiotics in therapeutic range in the group of patients, in which the dose for individual patients was consulted and in the group without any consultation. In the group where the dose was adjusted based on consultations, the patients had significantly higher percentage of trough levels in optimal range (59% vs. 89%). Only 40% of patients had optimal initial dose in the group without consultation; in the group with the consulted dose, it was more than 80% of patients. Fonzo-Christie et al. (2014) evaluated the implementation of the gentamicin dose recommendations for new-borns in 1 year-long prospective monitoring. One-year long study included two groups of new-borns. In the first group, the recommendations of dosage regimens for individual patients were implemented; in the second group, these recommendations are not applied. Trough concentrations were compared in both groups in the study. Occurrence of target concentrations was significantly higher in the group in which the recommended doses were applied (once daily, prolonged interval) (68.5% versus 33.0%). Probability of greater number of optimal concentrations also increased with the use of the recommended dosage regimens once daily.

For most patients in our prospective study, administration with a prolonged dose interval once daily was preferred with gentamicin dose adjustment. Administration once daily maximized the concentration-dependent effect of aminoglycosides, as well as the post-antibiotic effect. This regimen is generally accepted in hospitalized patients on basic beds, as well as in patients hospitalized in intensive care units. Target concentrations are more easily reached by the dosage regimen with prolonged interval. In the meta-analysis of Barza et al. (1996), reduction in the risk of nephrotoxicity was confirmed, but there was no significant difference in reducing the risk of ototoxicity and decreasing mortality. Higher efficiency was demonstrated in patients without pre-existing renal insufficiency, and finally, administration once daily was lower in cost. The dosage regimen with the prolonged interval reduces the probability of high trough concentrations responsible for any adverse events (Nezic et al., 2014). Radigan et al. (Radigan et al., 2010) prefer administration of aminoglycoside antibiotics over a prolonged interval even in the critically ill patients in intensive care units. In treatment by gentamicin, the benefit of a regimen with prolonged interval is greater when combined with therapeutic monitoring of levels, particularly in critically ill patients who have difficulty achieving effective peak concentrations (Wong et al., 2014).

Results of this work, in line with the results of studies by other authors', have significantly demonstrated the importance of individualized dosage regimens at the beginning of the therapy and the importance of therapeutic monitoring of levels.

CONCLUSION

Gentamicin, as an aminoglycoside antibiotic has still its place in the anti-infective therapy of hospitalized patients. Safe and effective administration of gentamicin requires reaching optimal residual and peak levels within the desired therapeutic range. Adjustment of dosage regimens by the clinical pharmacist for individual patients immediately at the beginning of therapy will provide for administering sufficient doses of antibiotics at the beginning of therapy, which is a precondition for a successful anti-infective therapy. Therapeutic monitoring of levels enables administration of sufficient doses of gentamicin at the beginning of therapy without fear of any adverse events. On the other hand, TDM identifies the usage of inadequate dosage regimens, which do not take the pharmacokinetic parameters into consideration and decreases the risk of under dosing.

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