PARAMETERS OF VANCOMYCIN PHARMACOKINETICS IN POSTOPERATIVE PATIENTS WITH RENAL DYSFUNCTION: COMPARING THE RESULTS OF A PHARMACOKINETIC STUDY AND MATHEMATICAL MODELING

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Mathematical modeling of pharmacokinetic (PK) and pharmacodynamic (PD) parameters essential for establishing correct dosing regimens is an alternative to pharmacokinetic studies (PKS) adopted in the clinical setting. The aim of this work was to compare the values of PK parameters for vancomycin obtained in an actual PKS and through MM in postoperative patients with kidney injury. Our prospective study included 61 patients (47 males and 14 females aged 60.59 ± 12.23 years). During PKS, drug concentrations at steady state C_{trough} and C_{peak} were measured by high-performance liquid chromatography followed by the calculation of the area under the plasma concentration-time curve AUC_{24}. For mathematical modeling, a single-compartment model was employed; PK parameters were estimated using R 3.4.0. The values of Ctrough measured 48 h after the onset of antibiotic therapy during PKS were significantly lower than those predicted by MM (p = 0.004). In a group of patients with acute kidney injury (AKI), AUC_{24} measured at the end of treatment was significantly higher than its value predicted by MM (p = 0.011). The probability of achieving the target AUC_{24} to MIC ratio of over 400 μg•h /ml is higher in the group of patients with C_{trough} = 10–15 μg /ml. Our findings confirm that the use of MM in postoperative patients with renal dysfunction is limited and therapeutic drug monitoring should be used instead.

Keywords: pharmacokinetic study, vancomycin pharmacokinetics, mathematical modeling, acute kidney injury, surgical patients

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ПАРАМЕТРЫ ФАРМАКОКИНЕТИКИ ВАНКОМИЦИНА У БОЛЬНЫХ С НАРУШЕНИЕМ ФУНКЦИИ ПОЧЕК В ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ: СРАВНЕНИЕ РЕЗУЛЬТАТОВ ФАРМАКОКИНЕТИЧЕСКОГО ИССЛЕДОВАНИЯ И МАТЕМАТИЧЕСКОГО МОДЕЛИРОВАНИЯ

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В клинической практике возможной альтернативой фармакокинетическим исследованиям (ФКИ) является методика математического моделирования (ММ) фармакокинетических (ФК) и фармакодинамических (ФД) параметров для расчета доз антибактериальных препаратов. Целью исследования было сравнение параметров ФК ванкомицина, полученных на основе ФКИ и ММ, у пациентов с нарушением функции почек в послеоперационном периоде. В проспективное исследование был включен 61 пациент (47 мужчин и 14 женщин, возраст 60,59 ± 12,23 лет). В ходе ФКИ методом высокоэффективной жидкостной хроматографии определяли C_{trough}, C_{peak}, с последующим расчетом площади под фармакокинетической кривой ($ПФК_{24}$). Расчет параметров ФК при ММ проводили с помощью программы R 3.4.0 на основе однокомпартментной модели. По данным ФКИ значения равновесных C_{trough} через 48 ч от начала антибактериальной терапии были достоверно ниже значений, полученных при ММ (p = 0,004). В группе пациентов с острым почечным повреждением (ОПП) на момент завершения терапии значения $ПФК_{24}$ по данным ФКИ были достоверно выше (p = 0,011). Вероятность достижения целевого отношения $ПФК_{24}$ / МПК > 400 мкг•ч /мл выше в группе пациентов, где C_{trough} составляет 10–15 мкг/мл. Таким образом, результаты исследования подтверждают, что у больных с нарушением функции почек в послеоперационном периоде применение ММ имеет ряд ограничений и необходимо проведение терапевтического лекарственного мониторинга (ТЛМ).

Ключевые слова: фармакокинетическое исследование, фармакокинетика ванкомицина, математическое моделирование, острое почечное повреждение, пациенты хирургического профиля

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To deliver safe and effective treatment, a pharmacokinetic study (PKS) or therapeutic drug monitoring (TDM) can be recommended for patients receiving antibacterial drugs with a narrow therapeutic index. According to the international guidelines, vancomycin TDM should include measurements of its trough concentrations (C_{trough}) at steady state, the area under the time-concentration curve (AUC_{24}), and the ratio of AUC_{24} to the minimum inhibitory concentration (MIC) of the prescribed drug. There are a few limitations to the use of TDM in clinical routine often arising from the failure to obtain the sufficient number of blood samples to calculate AUC_{24} [1, 2].

In some clinical circumstances, TDM can be replaced with the mathematical modeling (MM) of drug pharmacokinetics. For a number of antibiotics, including vancomycin, aminoglycosides, and colistin, a starting dosing regimen can be generated by medical calculators exploiting mathematic modeling [3, 4]. The medical calculator for vancomycin is based on a single-compartment pharmacokinetic model and can predict the ratio of pharmacokinetic to pharmacodynamic parameters and the minimum inhibitory concentration (MIC) necessary to calculate an adequate drug dose considering the patient's age, sex, weight, and renal function [5, 6]. The use of different types of mathematical modeling in clinical routine reduces the need for TDM.

There is little information about the use of MM for predicting drug pharmacokinetics in different groups of patients. It is impossible to predict the biotransformation dynamics, the volume of distribution and the elimination rate of antibacterial drugs in patients with acute kidney injury in the early postoperative period. Among other important MM drawbacks are high equipment and software costs [7, 8].

The literature analysis does not allow firm conclusions as to whether MM can be safely used instead of TDM in different clinical circumstances because too few research works have been carried out to compare these two methods.

Therefore, to improve the method of pharmacokinetic MM, pharmacokinetic studies need to be carried out in different groups of patients. The data yielded by such research works will help to improve the efficacy and safety of vancomycin-based therapy.

The aim of this work was to compare the results of a pharmacokinetic study and mathematical modeling of vancomycin pharmacokinetics in surgical patients with acute kidney injury.

METHODS

This prospective observational study was carried out at the facilities of the University Clinical Hospital No. 1 of Sechenov First Moscow State Medical University in September 2016 through January 2018. The study protocol was approved by the local Ethics Committee (Protocol No. 05–16 dated May 18, 2016).

The study included 61 postoperative patients (47 males and 14 females) with septic complications. Their mean age was 60.59 ± 12.23 years. The patients were distributed into two groups depending on the presence of acute kidney injury (AKI) [9]: group 1 included patients with AKI (n = 35; 66.6%), group 2 included patients without AKI (the controls; n = 26; 33.4%). In group 1, mild and moderate kidney injury prevailed: stage 1 AKI was diagnosed in 19 (31.1%) patients; stage 2, in 13 (21.3%) patients; stage 3, in 3 (4.9%) patients. Details are presented in Table 1. The groups were comparable in terms of main clinical characteristics, but the patients representing the group with AKI were significantly older (p = 0.004). In the postoperative period, those patients had higher albumin levels than the controls (p = 0.047).

Vancomycin regimen

All patients with infectious complications received vancomycin (marketed as Edicin by Sandoz; Slovenia). The dosing regimen was 15 to 20 mg per 1 kg of body weight, as recommended by the clinical practice guidelines, with due account of the patients' kidney function as estimated by the Cockroft-Gault equation (creatinine clearance rate Cl_{cr}, ml/min). The maximum

Table 1. Clinical characteristics of patients included in the study

Clinical characteristics	Total n = 61	Without AKI n = 26 (44.8%)	With AKI n = 35 (55.7%)	p
	M ± SD	M ± SD	M ± SD	
Age, years	60.59 ± 12.23	55.46 ± 12.89	64.4 ± 10.33	0.004*
BMI, kg/m^2	27.4 ± 5.2	27.12 ± 6.1	27.29 ± 4.5	0.726
EF_0, %	59.02 ± 7.86	62.53 ± 6.74	56.89 ± 7.83	0.018*
$Cl_{Cr\,0}$, ml/min	96.48 ± 29.01	96.26 ± 24.76	96.64 ± 32.16	0.96
$Cl_{Cr\,1}$, ml/min	61.5 ± 27.2	81.51 ± 23.54	46.64 ± 19.1	< 0.0001*
$Cl_{Cr\,2}$, ml/min	85.98 ± 32.33	87.37 ± 33.52	84.95 ± 31.86	0.776
$Albumin_0$, mg/dl	41.21 ± 4.2	42.46 ± 4.35	40.29 ± 3.97	0.447
$Albumin_1$, mg/dl	33.56 ± 1.52	32.21 ± 2.84	44.57 ± 1.61	0.047*
Hospital stay, days	25.07 ± 15.069	26.77 ± 4.27	23.8 ± 1.17	0.451
MV, days	3.30 ± 1.75	3.00 ± 1.29	3.51 ± 0.887	0.736
Intensive care, days.	6.46 ± 1.187	6.5 ± 2.27	6.43 ± 1.23	0.977
Blood loss, ml	653.44 ± 604.65	512.1 ± 258.8	758.00 ± 754.66	0.118
Mortality, %	11 (18%)	4 (36.4%)	7 (63.6%)	0.454

Note: * significant differences, p_{value} < 0.05; BMI — body mass index; Cl_{Cr} — creatinine clearance rate (Cockroft–Gault equation); $Cl_{Cr\,0}$ — before the surgery; $Cl_{Cr\,1}$ — 2–3 days after the surgery; $Cl_{Cr\,2}$ — 7–10 days after the surgery; MV — mechanical ventilation; EF — ejection fraction.

daily dose of the drug did not exceed 2 g. Vancomycin was administered by intravenous drips for 60 min every 12 h [10]. Dosing adjustments were done 24 to 48 h later based on the estimated Cl_{cr}.

The patients with AKI received significantly lower daily doses of vancomycin in comparison with the patients without kidney disfunction (928.6 ± 275 mg and 1637.9 ± 515.8 mg, respectively; $p < 0.0001$). Therapy duration was 9.61 ± 3.8 days. It depended on the severity and site of infection, results of microbiological tests, and individual patient's tolerability. Therapy duration did not differ significantly between the groups and was 9.17 ± 3.6 and 10.19 ± 4 days for groups 1 and 2, respectively ($p = 0.353$).

Parameters of vancomycin pharmacokinetics measured by high-performance liquid chromatography during the pharmacokinetic study

Blood samples for the PKS were collected from all patients included in the study as recommended by the guidelines for vancomycin TDM [1]. To measure C_{peak} (60 min after the infusion) and C_{trough} (60 min before administering the next dose), blood samples were collected 48 hours after the onset of therapy (1) and upon its completion (2) [11].

Proteins contained in the samples were precipitated using methanol. Quantitative measurements were done on the high-performance liquid chromatography system Agilent 1260 equipped with a gradient pump, a degasser, an autosampler, and the tandem mass spectrometer Agilent 6460 (AgilentTechnologies; USA). For separation, the ZorbaxEclipse Plus-C18 2.1 × 50 mm 1.8 µm column and the Zorbax Eclipse Plus C18 12.5 × 2.1 mm 1.8 µm guard column were used.

AUC_{24} was calculated from the obtained values of C_{peak} and C_{trough} at steady state as a sum of different phases of drug pharmacokinetics using the trapezoidal rule [12]:

$$AUC_{24} = \frac{(Lintrap + Logtrap) \times 24}{\tau};$$

where *Lintrap* is the area under the time-concentration curve during the linear phase of drug infusion:

$$Lintrap = \frac{(C_{trough} + C_{peak}) \times T_{inf}}{2};$$

where T_{inf} is infusion time (h).

Logtrap is the area under the "logarithmic" phase of drug elimination:

$$Logtrap = \frac{(C_{peak} - C_{trough})\ \tau - T_{inf}}{\ln \frac{C_{peak}}{C_{trough}}};$$

where τ is time between the infusions (h).

Method of mathematical modeling

Mathematic modeling was done in R 4.3.0 [12]. We estimated the values of C_{peak}, C_{trough} and AUC_{24} using the equations describing the pharmacokinetic dynamics for the single-compartment model 48 h after the onset of therapy (1) and upon its completion (2) [13]:

$$C_{peak} = \frac{Dose \times 1 - e^{-T_{inf} \times K_{el}}}{T_{inf} \times V_d \times K_{el} \times \left(1 - e^{-\tau \times K_{el}}\right)};$$

$$C_{trough} = C_{peak} \times e^{-K_{el} \times (\tau - T_{inf})};$$

where *Dose* is a single dose of vancomycin (mg), T_{inf} is infusion time (h), τ is time between the infusions (h), K_{el} is the predicted elimination rate (h^{-1}), and V_d is the apparent volume of distribution (l/kg):

$$V_d = 0.7 \times M;$$

where M is the absolute weight of a patient (kg).

To calculate the predicted elimination rate, the following equation was used [14]:

$$K_{el} = 0.00083 \times Cl_{Cr} + 0.0044;$$

where Cl_{Cr} is creatinine clearance (ml/min) determined by the Cockroft-Gault formula:

$$Cl_{Cr} = \frac{[140 - age] \times body\ weight\ (\text{kg}) \times (10.05\ for\ women \text{ or } 10.23\ for\ men)}{blood\ plasma\ creatinine\ \left(\frac{\mu mol}{l}\right)}.$$

To calculate AUC_{24}, the trapezoidal rule was applied:

$$AUC_{24} = \frac{(Lintrap + Logtrap) \times 24}{\tau}.$$

Statistical processing was done in IBMSPSS Statistics 18.0. and R 3.4.0. In this work continuous variables with normal distribution are presented as a mean (M) and a mean square deviation (SD). Categorical data are presented as a median (Me) and an interquartile range (IQR). Departure from normality was estimated using the Shapiro–Wilk test. The significance of frequency differences was assessed using Fisher's exact test. The significance of differences in arithmetic means between the groups was tested by ANOVA. Apart from ANOVA, nonparametric tests were applied; differences in mean ranks were compared using the Mann–Whitney–Wilcoxon test. The differences were considered significant at $p < 0.05$. To establish correlations between clinically significant pharmacokinetic parameters C_{trough} and AUC_{24}, Spearman's correlation was applied.

RESULTS

The actual values of K_{el}^1 yielded by the PKS (samples collected 48 h after the onset of therapy and upon its completion) were significantly higher than values predicted by MM (0.109 (0.08–0.15) and 0.06 (0.04–0.072), respectively; $p < 0.0001$). The actual values of C_{trough}^1 at steady state were significantly lower than the values predicted by MM (11.32 (8.1–16.4) and 16.59 (14.03–24.8), respectively; $p = 0.004$). At the same time, the values of C_{trough}^2 measured by HPLC and those predicted by MM did not differ significantly. The actual and predicted values of AUC_{24} did not differ significantly 48 h after the onset of antibacterial therapy ($p = 0.715$). Upon therapy completion, the actual values of AUC_{24}^2 were significantly higher than its predicted values (564.04 (409.5–751.9) and 347.03 (267.43–479.99) respectively; $p = 0.011$) (Table. 2).

Parameters of vancomycin pharmacokinetics measured by HPLC and predicted by MM did not differ significantly between group 1 and group 2, except for the actual values of K_{el}^1 ($p = 0.037$) that was significantly higher in the patients with kidney injury (Table 2).

Parameters of vancomycin pharmacokinetics obtained through real measurements demonstrate the variability of C_{trough} and AUC_{24} both at the onset of therapy and upon its completion (Fig. 1). This can be explained by the specifics of vancomycin pharmacokinetics in the studied sample, given standard dosing regimens. However, the obtained range of PK values predicted by MM and the significant difference from the actual values mean that the use of MM in patients with acute kidney injury is limited.

Table 2. Vancomycin pharmacokinetics evaluated by HPLC and MM in the groups of patients with and without AKI 48 h after the onset of therapy and at the time of its completion

PK parameter	TDM	MM	Mann-Whitney-Wilcoxon test; *p*	TDM (*n* = 61)		Mann-Whitney-Wilcoxon test; *p*	MM (*n* = 61)		Mann-Whitney-Wilcoxon test; *p*
	(*n* = 61)	(*n* = 61)		AKI+ (*n* = 35)	AKI–		AKI+	AKI–	
	Me [IQR]			Me [IQR]			Me [IQR]		
Kel[1] (hour $^{-1}$)	0.109 [0.08–0.15]	0.06 [0.04–0.072]	< 0.0001	0.12 [0.1–0.14]	0.1 [0.06–0.131]	0.037	0.04 [0.04–0.07]	0.06 [0.06–0.077]	0.117
Kel[2] (hour $^{-1}$)	0.08 [0.05–0.14]	0.08 [0.063–0.102]	0.274	0.06 [0.05–0.15]	0.11 [0.07–0.13]	0.412	0.08 [0.05–0.15]	0.09 [0.07–0.11]	0.709
C_{trough}^{1} (μg/ml)	11.32 [8.1–16.4]	16.59 [14.03–24.8]	0.004	9.6 [6.9–15.0]	12.08 [8.8–18.27]	0.197	16.2 [14.2–19.7]	14.03 [13.24–18.04]	0.54
C_{trough}^{2} (μg/ml)	12.59 [8.5–22.8]	8.65 [5.9–12.06]	0.092	15.7 [6.6–25.8]	12.59 [9.1–21.7]	0.776	8.3 [6.08–11.6]	10.14 [5.7–12.5]	0.765
C_{peak}^{1} (μg/ml)	35.6 [31.2-37.2]	27.3 [24.2–32.2]	0.019	35.1 [30.9–37.8]	23.8 [21.3–31.4]	0.502	26.2 [15.8–27.2]	28.2 [26.6–32.8]	0.502
C_{peak}^{2} (μg/ml)	22.5 [18.6–30.7]	34.8 [31.7–41.9]	0.002	35.6 [31.9–40.7]	23.8 [21.3–31.4]	0.263	26.23 [24.11–28.1]	34.8 [30.1–43.1]	0.263
AUC_{24}^{1} (μg × h/ml)	484.08 [404.5–604.4]	459.72 [433.6–556.01]	0.715	465.7 [399.5–605.3]	530.8 [480.2–603.4]	0.263	462.8 [450.4–548.5]	458.38 [413.8–553.5]	0.709
AUC_{24}^{2} (μg × h/ml)	564.04 [409.5–751.9]	347.03 [267.43–479.99]	0.011	551.2 [397.02–786.6]	564.04 [421.9–721.58]	0.765	345.4 [255.5–393.2]	386.8 [273.8–481.5]	0.502

Note: 1 — 48 h after the onset of therapy; 2 — at the time of its completion.

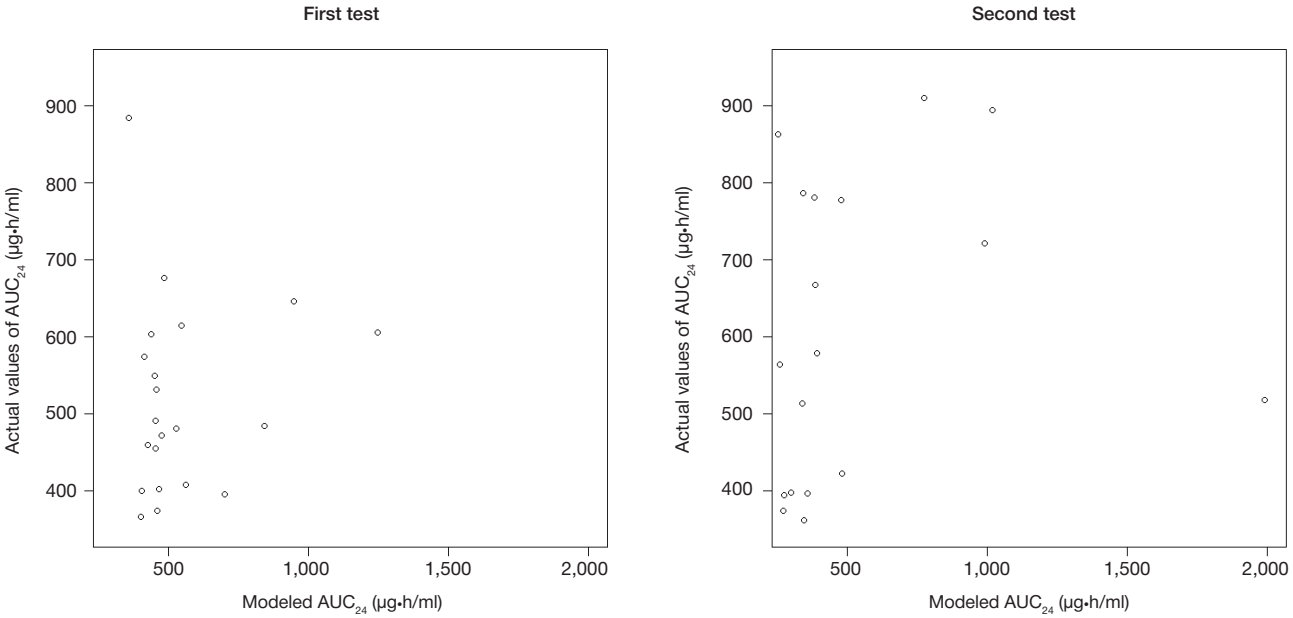

Fig. 1. The range of AUC_{24} values obtained through MM and high-performance liquid chromatography in postoperative patients with acute kidney injury 48 hours after the onset of therapy and upon its completion

In the patients with C_{trough} of 10–15 μg/ml at steady state, AUC_{24} was above 400 μg × h/ml both 48 h after the onset of therapy (Fig. 2) and at the time of its completion (Fig. 3). The correlation analysis revealed a positive correlation between the values of C_{trough} and AUC_{24} at steady state (r = 0.964; p < 0.001).

Predicting the probability of reaching the target PK/PD ratio

The values of AUC_{24} obtained through HPLC suggest that the target PK/PD ratio (AUC_{24}/MIC > 400) is highly probable if MIH equals 1 μg/ml (for *Staphylococcus aureus*). The exception is the group of patients in which C_{trough} is below 10 μg/ml; in this group the target PK/PD ratio was observed in 55% of patients. If MIC increases to 1.5 or 2 μg/ml, the probability of reaching the desired PK/PD ratio in the group of patients with C_{trough} = 10–15 μg/ml is reduced to 30%, and in the group with C_{trough} = 15–20 μg/ml, to 70% (Table 3). Hypothetically, the desired PK/PD ratio can be achieved at MIC = 2 μg/ml only if C_{trough} reaches 20 μg/ml or higher (Table 3).

The analysis of the predicted AUC_{24} to MIC ratio revealed that upon therapy completion the target PK/PD ratio of > 400 was observed mostly in the patients with C_{trough} above 10–15 μg/ml (Table 4).

DISCUSSION

Our study shows that if a standard approach to vancomycin dosing is applied in surgical patients with acute kidney injury, the actual values of C_{trough} measured by HPLC 48 h after the onset of therapy are significantly different from the values predicted by MM (11.32 (8.1–16.4) and 16.59 (14.03–24.8) μg/ml, respectively; $p = 0.004$).

The obtained results are consistent with the findings of other researchers who observed the high variability of pharmacokinetic parameters and the ratio of AUC_{24}/MIC > 400 in the patients of intensive care units treated with standard doses of vancomycin [15, 16].

The differences in the results yielded by PKS and MM can be explained by the drawbacks of the majority of mathematical models. A single-compartment model exploits a fixed mean V_d value of 0.7 l/kg. Pharmacokinetic studies demonstrate that this value can range from 0.2 to 1.25 l/kg and depends on the volume of circulating blood, albumin levels, etc. K_{el} is calculated based on the clearance rate Cl_{cr} estimated by the Cockroft–Gault equation. At present there is no perfect formula for estimating the rate of drug elimination based on the levels of endogenous creatinine [17, 18].

Some authors believe that the use of standard nomograms and MM for predicting drug pharmacokinetics has a number of limitations. First, the majority of these methods were validated on the limited population of healthy volunteers or stable patients. Second, the target values of steady-state C_{trough} were thought to fall within the range of 5–10 μg/ml. At present, the range of these values has risen to 15–20 μg/ml as demonstrated by a number of microbiological studies [19, 20].

It is debatable whether high C_{trough} concentrations and AUC_{24}/MIC of 400 or above really need to be achieved. Local microbiological monitoring demonstrates that at MIC of 1 μg/ml or below C_{trough} does not have to be as high as 15–20 μg/ml [21].

Our retrospective study demonstrates that over 30% of patients reached the target ratio AUC_{24}/MIC of > 400 even at C_{trough} below 15 μg/ml. Regression analysis reveals that

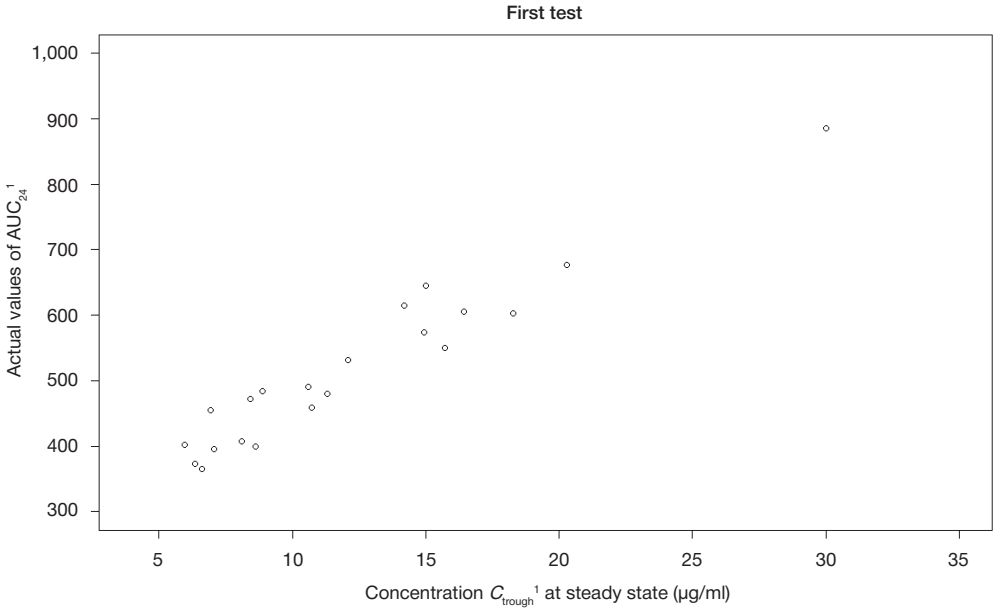

Fig. 2. Dependency of $AUC_{24}{}^1$ on the levels of steady-state $C_{trough}{}^1$ 48 hours after the onset of antibacterial treatment (HPLC)

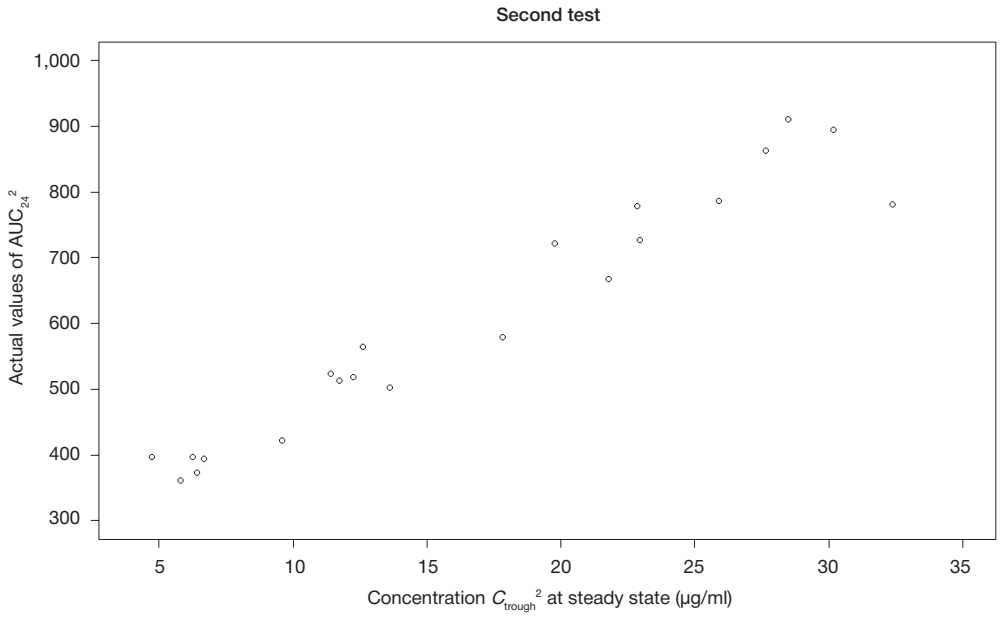

Fig. 3. Dependency of $AUC_{24}{}^2$ on the levels of steady-state $C_{trough}{}^2$ at the time of therapy completion (HLPC)

Table 3. Prediction of the AUC_{24}/ MIC ratio for *Staphylococcus aureus* 48 hours after the onset of vancomycin therapy

Value of C_{trough}, μg/ml	AUC_{24}, μg•h/ml			AUC_{24}/MIC > 400		
	M	min	max	MIC 1 μg/ml (%)	MIC 1.5 μg/ml (%)	MIC 2 μg/ml (%)
< 10	401.9753	365.676	484.0849	55	0	0
10–15	530.8875	459.4124	645.6017	100	30	0
15–20	603.4062	549.4891	605.2955	100	70	0
> 20	780.6152	676.4806	884.7498	100	100	50

Table 4. Prediction of the AUC_{24}/ MIC ratio for *Staphylococcus aureus* at the time of vancomycin therapy completion

Value of C_{trough}, μg/ml	AUC_{24}, μg•h/ml			AUC_{24}/MIC > 400		
	M	min	max	MIC 1 μg/ml (%)	MIC 1.5 μg/ml (%)	MIC 2 μg/ml (%)
< 10	395.1776	361.2053	421.9468	16	0	0
10–15	517.7069	502.5894	564.0411	100	0	0
15–20	650.2483	578.911	721.5856	100	50	0
> 20	783.8409	667.7073	910.8016	100	100	38

C_{trough} = 10.8 μg/ml is a predictor of the target AUC_{24}/MIC value above 400 [22].

In our study the patients treated with standard doses of vancomycin responded positively to treatment although their C_{trough} was 10–15 μg/ml (Table 2). The fact that they reached the target AUC_{24}/MIC ratio of > 400 can be explained by the microbiological monitoring carried out in our hospital (*S. aureus*, MIC of vancomycin < 1 μg/ml in 60–70% cases).

As MIC rises to 1.5 or 2 μg/ml, the efficacy of vancomycin treatment decreases in 30% or 70% of case, respectively.

The obtained data suggest that dosing adjustments aided by MM based on the results of the pharmacokinetic study involving measurements of C_{trough}, C_{peak} and AUC_{24} were more beneficial for the patients than dosing regimens based solely on the monitoring of C_{trough} [23].

Pharmacokinetic studies carried out in specific groups of patients are especially important in the development of a good mathematical model of vancomycin pharmacokinetics and selecting optimal dosing regimens. On a larger scale, the results of such studies can be used to build population models, which in turn requires more pharmacokinetic studies involving different cohorts of patients [24, 25].

CONCLUSIONS

Our study demonstrates that the predicted and actual values of vancomycin pharmacokinetics vary. The differences indicate the necessity of therapeutic drug monitoring in postoperative patients with kidney injury. Information about the actual C_{trough} values ensures better safety of vancomycin-based therapy in patients with acute kidney injury. The efficacy of the antibacterial treatment is constrained by the sensitivity of the infectious agent (MIC). For a better outcome, the AUC_{24}/MIC ratio should be calculated. Further pharmacokinetic studies of vancomycin are necessary to improve the method of mathematical modeling for postoperative patients with acute kidney injury.

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