
Case report**THE INFLUENCE OF AUGMENTED RENAL CLEARANCE ON VANCOMYCIN BLOOD CONCENTRATIONS IN PATIENTS WITH TRAUMATIC BRAIN INJURY: CASE REPORT****Running title: Augmented renal clearance and vancomycin**

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Abstract

Traumatic brain injury is a severe condition frequently complicated with infections, hypermetabolism, and augmented renal clearance (ARC). The ARC is a phenomenon characterized by increased creatinine clearance above 130 mL/min/1.73m². This phenomenon has been associated with decreased blood concentrations of selected antibiotics, like vancomycin, probably causing treatment failure. Despite ARC's possible fatal consequences in our local medical community, it is rarely assessed. Patient with traumatic brain injury accompanied with secondary infection and augmented renal clearance accompanied with subtherapeutic vancomycin concentrations in the time of treatment is presented. Since concentrations of antibiotics are not routinely measured in Serbian hospitals, clinical practice adjustment and widely accepted method of antibiotics blood concentration measurement which is particularly important in critically ill patients is suggested. The clinical pharmacologist is a significant team member for the treatment of critically ill patients due to his/her expert knowledge of pharmacokinetics and drug interactions, especially important in this category of patients, contributing to positive clinical outcomes.

Key words: traumatic brain injuries; augmented renal clearance; vancomycin; pharmacokinetic

Introduction

Traumatic brain injury (TBI) is a critical state frequently accompanied by serious complications, and according to data from the United States, high mortality in patients with TBI accounts for about 40% of all deaths from acute injuries¹. It is estimated that sixty-nine million (95% CI 64–74 million) individuals worldwide experience TBI each year². Sepsis and respiratory failure compromise recovery from TBI and result in prolonged hospitalizations and intrahospital mortality^{3,4}. Infections caused by gram-positive bacteria are the most common infections after craniotomy⁵.

Vancomycin, a tricyclic glycopeptide bactericidal antibiotic, is used to treat gram-positive bacterial multidrug-resistant infections (MDRI), including activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecium*^{5, 6}.

Patients who suffered TBI complicated with sepsis and/or ventilator-associated pneumonia, as any critically ill patient, can exhibit hypermetabolism and increased renal clearance³. Augmented renal clearance (ARC) is a phenomenon characterized by increased creatinine clearance above 130 mL/min/1.73m² and elimination of medications with predominantly renal excretion already described in patients with TBI^{4,7}. The mechanism driving ARC

is not clear⁴. Increased renal clearance has been associated with decreased blood concentrations of several antibiotics, including vancomycin^{7,8}, leading to treatment failure in neurosurgical patients. It is well known that low antibiotic concentrations increase the possibility of resistant bacteria appearance⁵. Therefore, maintaining appropriate antibiotic concentrations in patients after neurosurgical interventions is very important for effective antimicrobial treatment⁵. Vancomycin therapeutic monitoring is recommended since trough vancomycin concentrations, i.e. concentration of drug immediately before the next dose is administered, correlate well with its efficacy and safety⁵.

The aim of this case report was to point out the importance of therapeutic monitoring of vancomycin with special regard to the effect of ARC on vancomycin plasma concentrations in patients with TBI, which may compromise the therapeutic efficacy of this antibiotic.

Case presentation

A 19-year-old male patient with polytrauma was admitted to the intensive care unit (ICU) after suffering a car accident as a pedestrian. Evaluation on

admission revealed head injury (Figure 1A) comprising of open fracture of the skull base, massive cerebral edema, blood in four cerebral ventricles, the left temporomandibular joint fracture, and lung contusion. Otherwise, the patient was healthy in the preadmission period. Immediately after ICU admission, the patient underwent decompressive bifrontal craniotomy (Figure 1B). The patient developed chronic ischemia throughout the bilateral frontal region (Figure 1C).

Inflammatory parameters were increased during the postoperative period in the intensive care unit. Empirical antimicrobial therapy included meropenem in dose of 1g/8h, vancomycin 1g/12 h, and 200 mg/day fluconazole. After eight days, sepsis caused by gram-negative bacteria was diagnosed. Therefore, tigecycline 50 mg/12 h was introduced after five days from initiation replaced with colistimethate sodium 3000000 i.j./8 h based on antibiogram. On the 14th day of vancomycin therapy, serum trough concentrations of vancomycin (the concentrations of vancomycin at the end of the 12 hours dose interval) were measured, and the obtained value was below therapeutic range concentrations (1.33 µg/ml) (Table 1). Vancomycin concentrations were measured by chemiluminescence mi-

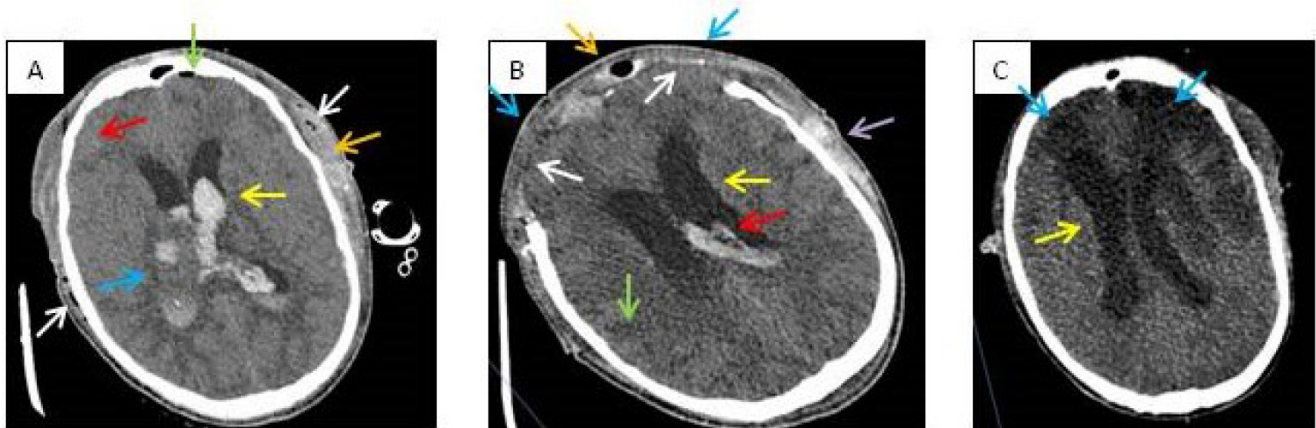


Figure 1: Multi-slice Computed Tomography scan without contrast agent application: axial section. In figure 1A, we can see intracerebral hematoma localized in the basal ganglia (blue arrow) with intraventricular bleeding that had been developing throughout the postoperative period (yellow arrow), diffuse brain parenchyma edema (red arrow), pneumocephalus (green arrow), bilateral subcutaneous emphysema temporally (white arrow) with subgaleal hematoma temporally left (orange arrow). Figure 1B presents the state after bilateral frontal osteoclastic craniotomy (blue arrow), left lateral ventricular dilatation (yellow arrow) with hemorrhagic contents (red arrow), diffuse brain parenchymal edema (green arrow) with extracranial herniation (white arrow), frontal epicranial hematoma with gas inclusion (orange arrow) and subgaleal hematoma on the left side (purple arrow). Figure 1C presented the state after bilateral frontal osteoclastic craniotomy: bilateral frontal diffuse chronic ischemia zone (blue arrow) and dilated ventricular system (yellow arrow).

cro-particles immunoassay (CMIA), ARCHITECT i1000SR Abbott Laboratories; Abbott Park, Illinois, USA). Subsequent dose adjustment of vancomycin to 1g/8 h was performed to achieve targeted therapeutic concentrations. On the 16th and the 19th day of vancomycin therapy, the achieved plasma concentrations were 2.37 µg/ml and 2.32 µg/ml, respectively. Vancomycin was stopped 19 days after its commencement, and it was changed with other antimicrobial drugs according to obtained antibiogram. Increased diuresis and low serum creatinine levels were recorded from the beginning of hospitalization, while blood urea levels were within the reference values (Table 1).

Discussion

Vancomycin pharmacokinetic characteristics

Here we presented the case of the young patient who suffered multiple organ injuries, including severe TBI complicated with an increased renal clearance which jeopardized the potential of therapeutic vancomycin concentrations. Vancomycin bypasses hepatic metabolism and undergoes renal excretion. Renal clearance is well correlated

to creatinine clearance^{9,10}. Vancomycin concentration generally increases proportionally with increasing dose⁹. Pharmacokinetic characteristics are presented in Table 2^{6,9}. Previous studies have demonstrated that critically ill patients have significant differences in pharmacokinetic parameters, including renal clearance⁷.

Vancomycin dosing in critically ill patients

Vancomycin dosing is based on patient weight and creatinine clearance (CrCl). Routine therapeutic drug monitoring is used to optimize its efficacy and minimize toxicity³. The recommended dose is 15 to 20 mg/kg of body weight every 8 to 12 h (not to exceed 2 g per dose)⁹. The dosing interval is based on the patient's estimated glomerular filtration rate⁶.

Rapid achievement of the target serum concentrations of vancomycin is necessary in severe infections by using the loading dose of 25–30 mg/kg of body weight⁹. In clinical practice, trough concentration monitoring (within 30 minutes before dosing) is mainly performed by measuring concentrations when the medication reaches a steady state. The steady-state is reached before the 4th

Table 1: Vancomycin concentrations, blood cell count, and biochemistry parameters measured on days 14, 16, and 19 after vancomycin administration. Low serum creatinine levels were recorded from the beginning of hospitalization, while blood urea levels were within the reference values. On day 14 of its administration, its blood concentration was below the therapeutic range (1.33 µg/ml)

Parameter	Day of vancomycin therapy		
	Day 14th	Day 16th	Day 19th
Vancomycin concentration [µg/ml]	1.33	2.37	2.32
White Blood Cell Count [g/L]	8.59 x 10 ⁹	7.02 x 10 ⁹	6.53 x 10 ⁹
Red Blood Cell Count [1/L]	3.14 x 10 ¹²	2.83 x 10 ¹²	3.05 x 10 ¹²
Hemoglobin [g/L]	88	79	85
Hematocrite [L/L]	0.28	0.24	0.26
Platelets [1/L]	436 x 10 ⁹	440 x 10 ⁹	399 x 10 ⁹
Blood glucose [mmol/L]	5.9	5.7	6.3
Blood urea [mmol/L]	6.6	6.1	6.7
Creatinine* [µmol/L]	46	34	40
Creatinine clearance [ml/min]**	242	328	279
Protein (total) [g/L]	58	51	50
C-Reactive Protein. [mg/L]	225.36	146.06	95.59

*Serum creatinine levels were below referent range; **Creatinine clearance calculated based on Cockcroft-Gault formula.

Table 2: Pharmacokinetic characteristics of vancomycin^{6,9}

Bound in plasma (%)	30
Volumen of distribution (L/kg)	0.39 ± 0.06
Clearance (ml/min/kg)	0.79 + 0.22
Half-life (h)	4–6
Urinary excretion *(%)	75–90

*through glomerular filtration in patients with normal renal function

dose if the dosing interval is every 12 h and before the 3rd dose for patients with dosing intervals > 24 hours¹¹. It is recommended that trough serum vancomycin concentrations always be maintained at > 10 µg/mL to avoid the development of resistance and maximize the bacteriological effect¹¹. For severe infections, vancomycin blood levels of 15–20 µg/mL are recommended⁶.

Expected serum concentrations after intermittent intravenous infusion of multiple doses of 1 g vancomycin (15 mg/kg) for 60 minutes are 50–60 µg/mL immediately after the injection, 11 hours after application, those levels fall to 5–10 µg/mL in patients with normal renal clearance⁹. Clinical experience indicates that total daily doses > 4000 mg of vancomycin are associated with an increased risk of nephrotoxicity⁷. After the 5th day of therapy, the risk of vancomycin caused acute kidney injury is generally increased¹². Trough concentrations > 20 µg/mL may result in vancomycin-induced nephrotoxicity and rarely ototoxicity¹³, while vancomycin levels of 37–152 µg/mL have been associated with ototoxicity⁶.

Current international dosing guidelines recommend that the value of the ratio of the 24-hour area under the vancomycin concentration – time curve (AUC_{0–24}) and minimum inhibitory concentration (MIC) should be 400–600 for invasive MRSA infections^{14, 15}. Previous expert guidelines recommended monitoring trough concentrations as a surrogate marker for the AUC/MIC ratio since it is difficult in the clinical setting to obtain multiple serum vancomycin concentrations to determine the AUC^{15,16}. A minimum target concentration of 15–20 µg/mL would be required to achieve AUC_{0–24}: MIC ≥ 400 for invasive MRSA infections in adults¹⁴. Expert guidance indicates that the fre-

quency of monitoring is based on clinical assessment, and daily monitoring should be performed in hemodynamically unstable patients. In contrast, weekly monitoring is suitable for hemodynamically stable patients¹⁵.

Augmented renal clearance and optimization of antimicrobial therapy

The process of optimizing antimicrobial therapy is a huge challenge for intensive care medical doctors, and previous studies have shown that in critically ill patients antimicrobials show significant inter- and intraindividual pharmacokinetic variability^{7,17,18}. The differences in pharmacokinetic parameters, including renal clearance, are acknowledged in studies⁷. High variability of plasma and tissue exposure to vancomycin in septic patients requires therapeutic monitoring of the medication¹². Inadequate antibiotic dosing can lead to low drug exposure and therapeutic failure and antimicrobial resistance, or high drug exposure, leading to an increased risk of toxicity^{5,17}.

Increased renal clearance (CrCL > 130 mL/min/1.73 m²) is present in more than 70% of patients with TBI^{3,14}. The ARC causes unexpectedly lower vancomycin concentrations, leading to suboptimal drug exposure and inadequate treatment¹⁹. The underlying mechanisms of ARC are uncertain, although critically ill patients, including patients with traumatic brain injury, often require aggressive fluid therapy during treatment^{3,17}. Tubular and neuroendocrine changes contribute to the development of ARC¹⁷. ARC is associated with the age < 50 years, male sex, high diastolic blood pressure, trauma, sequential organ failure assessment score ≤ 4, absence of diabetes, and ICU stay²⁰.

In patients with TBI and subarachnoid hemorrhage, a systemic inflammatory response occurs with increased cytokines and pro-inflammatory mediators, unified with aggressive fluid and hemodynamic changes leading to the variation of renal perfusion and glomerular filtration¹⁰. Identification of patients with ARC is essential as they may have an elevated renal function in the presence of normal serum creatinine concentrations²¹. Standard mathematical estimates of glomerular filtration rate, such as Cockcroft-Gault, are insufficiently reliable in this case²². Young patients otherwise healthy before suffering polytrauma are at greatest risk for developing ARC, which leads to suboptimal

plasma concentrations of antibiotics¹⁷. Endothelial dysfunction with the expansion of the interstitial space, disturbing the pharmacokinetics of hydrophilic antimicrobials such as vancomycin, cause a significant increase in the volume of distributions of these drugs in sepsis and other critical illness¹⁷.

Due to ARC, suboptimal exposure to critical medications, including beta-lactams and vancomycin, increases the risk of treatment failure¹⁰. Beta-lactam antibiotics extravascular accumulation in tissue compartments happens despite normal or even low medication serum concentrations¹⁰. Further increase of the antibiotics dose based on lower serum concentrations poses a risk for overexposure and neurotoxicity¹⁰. When adjusted vancomycin doses calculated based on standard values of CrCl (120 mL/min/ 1.73 m²) are applied, it may lead to subtherapeutic trough serum concentrations and potential treatment failure³.

In a retrospective study, 154 neurosurgical patients were treated with vancomycin to prevent or treat intracranial infections⁵. After surgery, the group with external ventricular drain had significantly lower trough serum vancomycin concentrations. Both groups, with or without external drainage, achieved vancomycin trough levels were suboptimal⁵. Greater vancomycin clearance was observed in patients with an external ventricular drain, and these patients required a 1.5 times higher daily dose than patients without TBI⁵. In 20 critically ill patients with head injury trauma, burns, neurological diseases, sepsis, two parameters of renal function, tubular anionic secretion, and reticular tubular reabsorption were significantly increased²³. Prospective, a single-center, observational cohort study included 93 critically ill patients, of which 40% developed ARC (with a median measured ClCr of 159 ml/ min/1.73 m²)¹⁰. The serum creatinine had similar values among all patients regardless of the presence of ARC¹⁰. Vancomycin trough concentrations in patients with ARC were significantly lower than those without ARC. The therapeutic plasma concentrations were achieved on day 1 in only 10.8% of patients in the ARC group and 51.6% on day 3 of therapy²². This information indicates that patients with ARC achieve lower vancomycin concentrations and are more likely to have subtherapeutic concentrations when standard dosing strategies are applied¹⁰.

CMIA method for determining antibiotic blood

concentrations in patients hospitalized in Serbia is used, but it is far from daily routine. Clinical pharmacologist is a medical specialist who can provide, among other services, valuable contribution in the treatment of critically ill patients due to his/her expertise knowledge of pharmacokinetics and drug interactions, especially important for this category of patients, contributing to positive clinical outcomes (24, 25). He/she realizes this as a member of the team, through close cooperation with medical doctors who treat critically ill patients and laboratory staff who introduce new methods for antimicrobial drug concentration monitoring on his/her proposal.

Conclusion

Vancomycin is the first-line treatment for gram-positive bacterial infection after neurosurgery, and its trough concentration are most probably related to its therapeutic efficacy. It is mainly excreted by the kidneys, and ARC has been confirmed as one of the causes of treatment failure caused by the insufficient concentration of vancomycin in the blood of the patients with TBI. Further investigations of the pharmacokinetics of vancomycin in these patients are necessary, as well as the implementation of routine therapeutic drug monitoring in the hospitals since further optimization of its dosing is needed. This is best realized through the cooperation of intensive care physicians, clinical pharmacologists and laboratory staff in charge of measuring the concentration of antimicrobials in the blood of hospitalized patients.

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