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Acta Fac. Pharm. Univ. Comen. LXII, 2015 (2): 1-4.
ISSN 1338-6786 (online) and ISSN 0301-2298 (print version),
DOI: 10.1515/afpuc-2015-0025

ACTA FACULTATIS PHARMACEUTICAE UNIVERSITATIS COMENIANAE

An adjustment of vancomycin dosing regimen for a young patient with augmented renal clearance: A case report

Úprava dávkového režimu vankomycínu pre mladého pacienta so zvýšeným renálnym klírensom: Kazuistika

Original research article/Review

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Received September 16, 2015, accepted: October 15, 2015

Abstract Augmented renal clearance (ARC) is a recently reported condition in pathophysiology of critically ill patients in the intensive care unit. ARC refers to the enhanced renal elimination of circulating solutes. These patients are either young or previously healthy people who have undergone surgery or multiple trauma.
This case report describes an adjustment of dosing regime of vancomycin to a young patient, who demonstrated ARC with severe polytrauma, overcome crush syndrome and sepsis. This 16-year old male patient was crushed by a tractor, which caused severe tissue damaged in the right lower limb. He gradually developed a serious crush syndrome. When kidneys resumed their function, creatinine clearance reached the value that indicated ARC (339.81 mL/min/1.73 m^2). Vancomycin was included in the patient's treatment regime by administering conventional dose of 1 g per 12 hours. The residual measured levels were very low. The dose of vancomycin had to be adjusted to double and then to triple the conventional dose. Without the therapeutic drug monitoring (TDM) and subsequent interpretation of the results by the clinical pharmacists, such high doses would not have been considered for administration.
ARC responds strongly to sub-therapeutic serum vancomycin levels. Our case report confirms the significance of TDM and the consecutive interpretation of the results in critically ill patients.

Slovak abstract Zvýšený renálny klírens sa nedávno popísal ako stav v patofyziológii kriticky chorých pacientov na jednotkách intenzívnej starostlivosti. Zvýšený renálny klírens predstavuje zvýšenú obličkovú elimináciu látok. Vyskytuje sa u mladých pacientov, pred tým zdravých, ktorí podstúpili chirurgický zákrok alebo utrpeli traumu.
Kazuistika popisuje úpravu dávkového režimu vankomycínu u mladého pacienta s ťažkou polytraumou, prekonaným crush syndrómom a sepsou, u ktorého sa demonštroval zvýšený renálny klírens. Tento 16 ročný mladý muž bol privalený traktorom, u ktorého došlo k devastačným poraneniam pravej dolnej končatiny. Postupne sa u neho vyvinul crush syndróm. Keď sa obnovili obličkové funkcie, klírens kreatinínu dosahoval vysoké hodnoty, ktoré spadali do hodnôt zvýšeného renálneho klírensu (339,81 ml/min/1,73 m^2). Vankomycín bol súčasťou antibiotickej liečby a začal sa podávať v konvenčnom dávkovaní 1 g každých 12 hodín. Namerané reziduálne hladiny boli veľmi nízke. Dávka vankomycínu sa musela upraviť na dvojnásobnú až trojnásobnú dávku konvenčnej dávky. Bez terapeutického monitorovania hladín a následnej interpretácie výsledkov klinickým farmaceutom by nebolo možné podať vysoké dávky vankomycínu.
Subterapeutické hladiny sú dôsledkom zvýšeného renálneho klírensu. Naša popísaná kazuistika potvrdzuje význam terapeutického monitorovania hladín liekov a interpretáciu výsledkov u kriticky chorých pacientov.

Keywords *Vancomycin – Augmented renal clearance (ARC) – Therapeutic drug monitoring (TDM)*

Kľúčové slová: *vankomycín – zvýšený renálny klírens (ARC) – terapeutické monitorovanie liekov (TDM)*

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INTRODUCTION

Vancomycin has been widely used for many years as a first-choice antibiotic for nosocomial infections caused by gram-positive bacteria. Achieving the correct serum level can be a difficult task, particularly in severely septic patients who manifested augmented renal clearance (ARC) (1).

ARC is a recently reported condition in pathophysiology of critically ill patients in the intensive care unit (ICU) (2). ARC refers to the enhanced renal elimination of circulating solutes. These patients are either young or previously healthy people who have undergone surgery or multiple trauma. Baptista et al. (6) have considered ARC value of creatinine clearance value above 130mL/min/1.73 m^2. According to Udy (2010), augmented CrCl was defined as >150 mL/min/1.73 m^2 in women and >160 mL/min/1.73 m^2 in men (8, 9). It might induce sub-optimal concentrations of drugs eliminated by glomerular filtration mainly antibiotics (3, 4).

The incidence rate of ARC in patients with different medical conditions in relation to vancomycin levels or possible risk factors were analysed (2, 4). Literature survey revealed that only few reports are available on individual case reports of patients with ARC. Cook et al. (2013) have recently reported that the patient with severe traumatic brain injury can be treated with vancomycin (7). In this case report, we have described our study on a very young patient with devastating injuries to the lower extremities without traumatic brain injury, who have overcome crush injury.

CASE REPORT

A 16-year old male patient (weight 89 kg, height 182 cm) was brought by the Air Rescue Service to the Teaching Hospital Nitra, Slovak Republic, after he had been crushed by a tractor. In the clinical picture, devastating injury of the right lower limb with the oppression of the nerve vascular bundle dominated. Condition of this patient revealed an open fracture of the right tibia and a number of lacerations and contusions all over his body. He gradually developed a serious crush syndrome with the washout of large amounts of myoglobin from the damaged tissues of the right lower limb, renal impairment and an acute renal insufficiency. The patient was continually dialysed. Three days later, the trauma surgeon indicated an exarticulation of the right lower limb because of extensive gangrene and the adverse effect of reperfusion syndrome on vital functions recovery. The patient's condition was concluded as a serious polytrauma, crush syndrome and septic shock. Gradually, the complex support of vital functions led to the stabilisation of the patient, the diuresis was restored and kidneys were resumed their function. Creatinine clearance during the sepsis state reached the values that indicated the ARC. ARC was recorded (138.04 mL/min/1.73 m^2) at the day 29 after hospitalisation and reached the highest values (339.81mL/min/1.73 m^2) at the days 41, 46, 49 and 51 after hospitalisation.

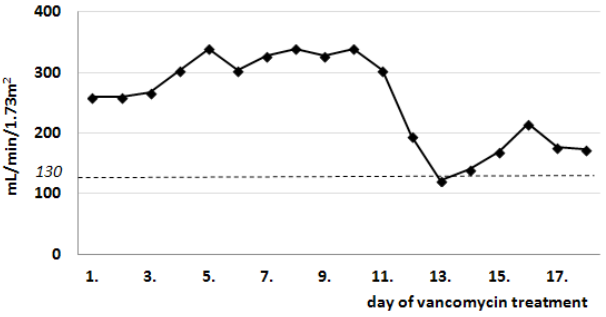

Figure 1: Evolution of estimated creatinine clearance (mL/min/1.73 m^2 - Cocroft-Gault) during vancomycin therapy.

The values of creatinine clearance (Cocroft-Gault) in response to administration of vancomycin are depicted in Figure 1.

During the hospitalisation in the ICU, as a precautionary treatment, different antibiotics and antimycotics were administered to the patient, which included amikacin, ampicillin/sulbactam, ceftazidime, ciprofloxacin, colistin, imipenem, penicillin and piperacillin/tazobactam in order to treat the infection caused by *Acinetobacter baumannii, Corynebacterium xerosis, Enterobacter cloacae, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Pseudomonas mendocina,* coagulase-negative *Staphylococcus (methicillin resistant), Stenotrophomonas maltophilia, Candida parapsilosis* and *Candida dubliniensis.*

During the ARC, the patient's hemoculture test showed positive for *Staphylococcus hominis*, coagulase-negative staphylococcus, which is resistant to the beta-lactam antibiotics. Vancomycin was included in the patient's treatment regime from the day 42 after hospitalisation. Physicians in the ICU started administering vancomycin to the patient in a conventional dosing regime of 1 g per 12 hours. The residual measured concentration of vancomycin was very low – 1.5 mg/L. Clinical pharmacist doubled the dose of vancomycin to 2 g per 12 hours. After one day, the residual concentration reached the required level 15.43 and 9.93 mg/L. Two days later, increase in the creatinine clearance was observed, and the vancomycin concentration decreased to 4.88 mg/L. The dose of vancomycin had to be readjusted to triple the original dose to 2 g per 8 hours (67 mg/kg/day). For determination of the required dose adjustment according to the patient's pharmacokinetic parameters, the *Abbottbase Pharmacokinetic Program* (Figure 2) was used. After this dose readjustment, the vancomycin concentration reached 18.7 mg/L. Vancomycin at this dose was administered to the patient for one more day. After the concentration reached 21.90 mg/L, the dosing schedule was adjusted to 2 g of vancomycin per 12 hours.

The patient was hospitalised in the ICU for more than two months. The whole healthcare team was efficiently involved to save the patient's life. Long-term hospitalisation in the ICU automatically represented a potential risk of nosocomial

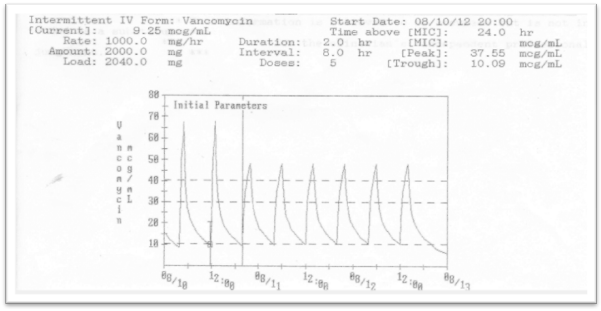

Figure 2: The calculated dose and predictions of levels according to Abbottbase Pharmacokinetic Program for our patient with ARC.

infections. Vancomycin was one of the last antibiotics that were administered to the patient. He was transferred in a good health state to the rehabilitation centre, where he has learned to use his prosthetic.

DISCUSSION

In this case report, we have described a severe pathophysiology of a young patient with severe polytrauma, overcome crush syndrome and sepsis, who demonstrated ARC. This patient was treated with conventional doses of vancomycin, which proved to be insufficient to reach the desired effective therapeutic concentration levels. The effective concentrations of vancomycin were achieved after increasing the doses to triple the amounts of the conventional dose.

The management of nosocomial infection in the ICU represents an ongoing challenge for critical care clinicians. The critically ill represent a unique population, either presenting with infection complicated by systemic inflammation (sepsis) or being predisposed to such complications by the virtue of the underlying disease process (5).

In the young patient with polytrauma after the kidney insufficiency because of the crush syndrome, the renal functions were restored to such an extent that the creatinine clearance reached the high levels which were determined as augmented renal clearance (ARC).

From a pharmacokinetic point of view, ARC can result in elevated renal elimination and sub-therapeutic plasma concentrations of medicinal products. Multi-trauma has already been identified as a significant risk factor for ARC. Current evidence suggests that young patients without pre-existing co-morbidity or organ dysfunction who present with trauma are most likely to manifest ARC (9, 10).

Without the therapeutic drug monitoring (TDM), interpretation of the results and the proposal of the dosing schedule by the clinical pharmacists, such high doses would not have been considered for administration.

This situation is usually ignored by clinicians; however, even though patients are underdosed, it should be considered a major cause of treatment failure and emergence of bacterial resistance in critically ill patients with sepsis (1). TDM enabled administration of the high effective doses of vancomycin without the apprehension of the adverse events occurrence. TDM should be considered in this setting to allow the optimisation of antibiotic exposure (6).

CONCLUSION

In conclusion, ARC is strongly associated with sub-therapeutic serum vancomycin levels and this case report clearly shows the importance of higher doses of vancomycin in treating such critical ill patients. ARC appears in young males with trauma and without previous severe disease.

Our case report confirms the establishment of efficient therapeutic dose of vancomycin without the TDM and the consecutive interpretation of the results in critically ill patients would not be possible. In such patients, the effective concentrations of vancomycin would not be achieved because of the apprehension of the possibility of adverse drug reactions occurrence, and their treatment would, therefore, not be effective.

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