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Augmented renal clearance in critically ill patients: incidence, associated factors and effects on vancomycin treatment

Incremento da depuração renal em pacientes gravemente enfermos: incidência, fatores associados e efeitos no tratamento com vancomicina

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ABSTRACT

Objective: An augmented renal clearance has been described in some groups of critically ill patients, and it might induce sub-optimal concentrations of drugs eliminated by glomerular filtration, mainly antibiotics. Studies on its occurrence and determinants are lacking. Our goals were to determine the incidence and associated factors of augmented renal clearance and the effects on vancomycin concentrations and dosing in a series of intensive care unit patients.

Methods: We prospectively studied 363 patients admitted during 1 year to a clinical-surgical intensive care unit. Patients with serum creatinine >1.3mg/dL were excluded. Creatinine clearance was calculated from a 24-hour urine collection. Patients were grouped according to the presence of augmented renal clearance (creatinine clearance >120mL/min/1.73m^2), and possible risk factors were analyzed with bivariate and logistic regression analysis. In patients treated with vancomycin, dosage and plasma concentrations were registered.

Results: Augmented renal clearance was present in 103 patients (28%); they were younger (48±15 versus 65±17 years, p<0.0001), had more frequent obstetric (16 versus 7%, p=0.0006) and trauma admissions (10 versus 3%, p=0.016) and fewer comorbidities. The only independent determinants for the development of augmented renal clearance were age (OR 0.95; p<0.0001; 95%CI 0.93-0.96) and absence of diabetes (OR 0.34; p=0.03; 95%CI 0.12-0.92). Twelve of the 46 patients who received vancomycin had augmented renal clearance and despite higher doses, had lower concentrations.

Conclusions: In this cohort of critically ill patients, augmented renal clearance was a common finding. Age and absence of diabetes were the only independent determinants. Therefore, younger and previously healthy patients might require larger vancomycin dosing.

Keywords: Creatinine; Vancomycin/therapeutic use; Vancomycin/pharmacokinetics; Metabolic clearance rate; Sepsis/drug therapy

INTRODUCTION

Critically ill patients frequently develop a hyperdynamic cardiovascular pattern as a consequence of systemic inflammatory response. High cardiac output could be associated with increased perfusion in different organs, including the kidneys. In this way, increases in the glomerular filtration rate could ensue, with subsequent enhanced renal elimination of circulating solutes. This phenomenon is known as renal hyperfiltration, or augmented renal clearance (ARC).[1] The syndrome is commonly defined by an increase in the

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creatinine clearance (Cl_{Cr}).[2] In the clinical practice, the Cl_{Cr} is usually estimated with the Cockcroft-Gault formula from creatinine plasma concentrations (estimated Cl_{Cr}), instead of calculating it after a 24-hour urine collection (24-h Cl_{Cr}). In critically ill patients, the agreement between both methods is poor.[3]

ARC in the critically ill is associated with some conditions, mostly trauma[4] and burns.[5] Nevertheless, its epidemiology, risk factors, and clinical characteristics have not been comprehensively investigated. Particularly, studies focused on general populations of critically ill patients are scarce. Most importantly, the increase in kidney function may decrease plasma concentrations of several drugs, involving such relevant therapeutic issues as antibiotic dosing.[6] The main concern is a lack of achievement of therapeutic concentrations of antimicrobial agents, which can lead to both treatment failures and generation of resistant bacteria.[7] In this respect, a vancomycin trough level <15μg/mL has been identified as an independent predictor of treatment failure.[8]

We studied these issues in a cohort of medical/surgical critically ill patients. Our objectives were as follows: (1) to describe the incidence of ARC on the day of admission; (2) to evaluate the ability of estimated Cl_{Cr}, compared to a 24-hour Cl_{Cr}, to diagnose ARC, as well as the agreement between both parameters; (3) to identify predictors of ARC; and (4) to assess the impact of ARC on the vancomycin plasma concentration and dosage.

METHODS

This is a prospective cohort study in consecutive patients admitted to a sixteen-bed mixed medical-surgical intensive care unit (ICU) during a period of 1 year, from October 1, 2011 to September 31, 2102. The exclusion criteria were age under 21 years, refusal to participate in the study, not having a bladder catheter in place, unavailable 24-hour urine collection, and plasma creatinine levels >1.3mg/dL. Our study was approved by the Institutional Review Board. As standard procedures were applied in the diagnosis, permission only to use the data was requested from patients or relatives.

On admission, demographic data (age, gender, weight, height), and main diagnostic categories (septic, postoperative, obstetric, trauma, and neurologic) were registered. Throughout the following day, Acute Physiological and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, the use of vasopressors, inotropes and diuretics, and the input/output of fluids were recorded. Additionally, a 24-hour urine sample was collected using a bladder catheter.

We measured arterial blood gases, (AVL OMNI 9, Roche Diagnostics, Graz, Austria), plasma and urinary [Na^+], [K^+] and [Cl^-] (Ion selective electrode, AEROSET, Abbott Laboratories, Abbott Park, Illinois, U.S.A), plasma albumin concentration (Bromocresol-sulfoftalein), lactate (Ion selective electrode, AVL OMNI 9), plasma and urinary levels of urea and creatinine (kinetic modification of the Jaffé reaction), and urine proteins.

The 24-hour Cl_{Cr} was calculated according the following formula: creatinine clearance (mL/min) = [urinary creatinine (mg/dL) x urinary output (mL/min)]/[plasma creatinine (mg/dL)]. The 24-hour Cl_{Cr} was adjusted to body surface area, estimated according to Mosteller:[9] body surface area = $\sqrt{}$weight (kg) x height (cm)/3,600.

The estimated Cl_{Cr} was calculated from plasma creatinine using the Cockcroft-Gault formula.[10]

In patients with suspected or confirmed gram-positive infections, vancomycin was initially administered as a loading dose (15mg/kg) followed by continuous infusion (30mg/kg/day) aimed at plasma concentrations of 15-25μg/mL.[11] If appropriate, dosage adjustments were performed on subsequent days. Daily doses of vancomycin were registered, and serum levels were measured on the first 3 days of treatment using a homogeneous enzyme immunoassay (VITROS VANC, Ortho-Clinical Diagnostics, Johnson & Johnson, Rochester, NY, USA).

Statistics

Patients were grouped according to the presence or absence of ARC (24-h Cl_{Cr} ≥120 or <120mL/min/1.73m^2, respectively). Data were analyzed for distribution by means of Kolmogorov-Smirnov test. Linear regression and Bland and Altman analysis were used for the evaluation of correlation and agreement between the different methods of calculation of Cl_{Cr}.[12] Comparisons between groups were performed with unpaired Student's *t*-test for parametric variables and Mann-Whitney *U*-test for non-parametric variables. Categorical parameters were compared with chi-square test. All variables with a p value <0.20 in bivariate analysis were entered in a logistic regression analysis with ARC as the outcome variable. Doses and plasma concentrations of vancomycin were compared by two-way repeated measures of ANOVA. A p value <0.05 was considered statistically significant.

RESULTS

Three hundred and sixty-three patients were included; 103 (28%) developed ARC. The clinical and epidemiological data of both groups are shown in table 1. Compared to patients without ARC, those with ARC were younger, had obstetric and trauma admissions more frequently, and showed lower APACHE II scores. There were no differences in SOFA score.

Estimated and 24-hour Cl_{Cr} were significantly correlated but showed poor agreement (Figure 1). Sensitivity and specificity of estimated Cl_{Cr} for the identification of ARC were 39.8 and 90.8%, respectively.

Patients with ARC had higher diuretic volumes and urinary elimination of electrolytes, and less use of furosemide and positive fluid balance. There were no differences in acid-base parameters, plasma electrolytes, fluid intake, and norepinephrine requirement. The urine protein/creatinine ratio was higher in patients without ARC (Table 2).

In the linear regression analysis, age and 24-hour Cl_{Cr} were significantly correlated (R^2=0.28, p<0.0001). Logistic regression analysis identified younger age and absence of diabetes as the only independent predictors of ARC (Table 3).

Table 1 - Clinical and epidemiological data in patients with and without augmented renal clearance

	Augmented renal clearance (N=103)	No augmented renal clearance (N=260)	p value
Gender (male)	49 (48)	54 (47)	0.96
Age (years)	48±15	65±17	<0.0001
Height (cm)	168±11	166±10	0.06
Actual weight (kg)	73±17	76±17	0.10
Ideal weight (kg)	62±12	60±11	0.12
Body area (m^2)	1.84±0.26	1.86±0.24	0.35
Comorbidities			
Hypertension	21 (20)	126 (48)	<0.0001
Ischemic cardiopathy	5 (5)	23 (9)	0.20
Cardiac failure	0 (0)	13 (5)	0.0208
Atrial fibrillation	6 (6)	46 (18)	0.0036
Diabetes mellitus	5 (5)	46 (18)	0.0015
COPD	3 (3)	17 (7)	0.1723
Smoking	13 (13)	52 (20)	0.0983
Cancer	33 (32)	87 (33)	0.795
APACHE II score	7 [4-11]	10 [6-14]	<0.0001
SOFA score	1 [0-2]	1 [0-3]	0.12
Mechanical ventilation	19 (18)	46 (18)	0.87
Shock	12 (12)	44 (17)	0.21
Diagnostic categories			
Postoperative	50 (49)	117 (45)	0.54
Septic	14 (16)	53 (20)	0.13
Obstetric	16 (16)	17 (7)	0.0006
Neurologic	10 (10)	33 (13)	0.43
Trauma	10 (10)	9 (3)	0.016
ICU mortality	4 (4)	20 (8)	0.19
Hospital mortality	4 (4)	20 (8)	0.19
ICU length of stay (days)	2 [1-4]	2 [1-4]	0.87
Hospital length of stay (days)	7 [5-11]	8 [5-15]	0.22

COPD - chronic obstructive pulmonary disease; APACHE II - Acute Physiology And Chronic Health Evaluation II; SOFA - Sequential Organ Failure Assessment; ICU - intensive care unit. Data are shown as number (%), mean±SD or median [IQR].

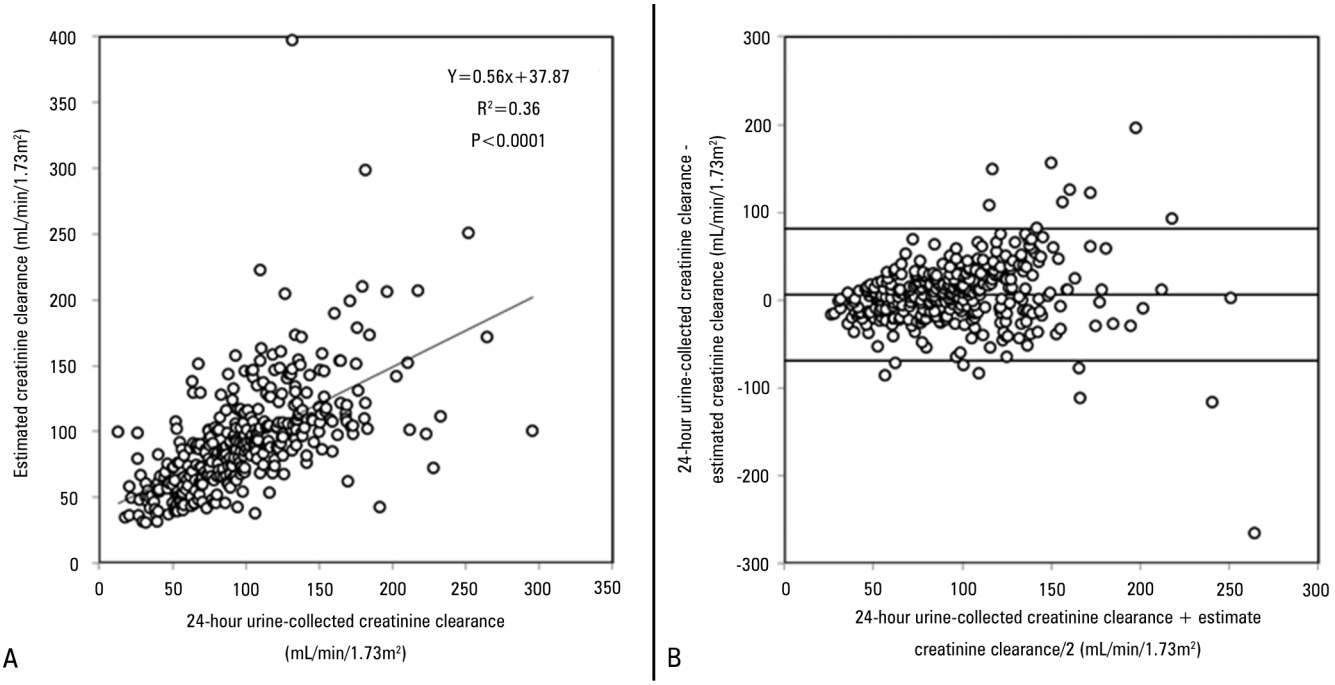

Figure 1 - Panel A) Linear regression analysis between 24-hour urine-collected creatinine clearance and estimated creatinine clearance. Panel B) Bland and Altman analysis between the 24-hour urine-collection creatinine clearance and estimated creatinine clearance. Lines represent the bias and the 95% limits of agreement.

Table 2 - Acid-base and renal parameters in patients with and without augmented renal clearance

	Augmented renal clearance (N=103)	No augmented renal clearance (N=260)	p value
Plasma creatinine (mg/dL)	0.7±0.2	0.9±0.2	<0.0001
Plasma urea (mg/dL)	25±11	34±15	<0.0001
Arterial pH	7.41±0.05	7.41±0.06	0.93
Arterial PCO_2 (mmHg)	37±7	38±8	0.65
Arterial PO_2 (mmHg)	99±27	93±30	0.12
Arterial [HCO_3^-] (mmHg)	23±3	23±4	0.50
Plasma [Na^+] (mEq/L)	136±4	136±4	0.78
Plasma [K^+] (mEq/L)	3.9±0.4	3.9±0.5	0.21
Plasma [Cl^-] (mEq/L)	105±5	104±6	0.33
Lactate (mmol/L)	1.6±0.6	1.7±0.8	0.15
Albumin (g/L)	2.6 ± 0.6	2.6±0.6	0.95
Urinary urea (g/day)	24.8±10.9	18.3±8.8	<0.0001
Urinary creatinine (mg/day)	1605±650	1039±432	<0.0001
24-hour Cl_{Cr} (mL/min/1,73m²)	155±33	78±25	<0.0001
Estimated Cl_{Cr} (mL/min)	126±48	80±29	<0.0001
Urinary [Na^+] (mEq/day)	255±147	187±129	<0.0001
Urinary [K^+] (mEq/day)	84±40	67±29	0.0004
Urinary [Cl^-] (mEq/day)	318±160	228±136	<0.0001
Urinary protein (g/day)	0.36 [0.19-0.69]	0.40 [0.22-0.71]	0.46
Infused fluids (mL/24 h)	3093±1104	3342±1508	0.13
Diuresis (mL/24 h)	2446±1337	1924±904	<0.0001
Fluid balance (mL/24 h)	648±1676	1433±1713	<0.0001
Norepinephrine	11 (11)	31 (12)	0.74
Furosemide	5 (5)	38 (15)	<0.001

24-hour Cl_{Cr} - creatinine clearance calculated from the 24-hour collection of urine; estimated Cl_{Cr} - creatinine clearance estimated from its plasma concentrations with the Cockcroft-Gault formula. Data are shown as number (%), mean±SD or median [IQR].

Table 3 - Logistic regression analysis with renal hyperfiltration as the outcome variable

Independent variable	OR	95%CI	p value
Age (years)	0.946	0.932-0.961	<0.0001
Diabetes mellitus	0.337	0.123-0.923	0.034

OR - odds ratio; 95%CI - 95% confidence interval.

Forty-four patients received vancomycin, and 12 of them had ARC. These patients showed lower plasma concentrations of the drug and required higher doses than patients without ARC (Figure 2). After 24 hours of treatment, plasma concentrations of vancomycin were inversely correlated with 24-hour Cl_{Cr}, and no patient with ARC reached the target through levels (Figure 3).

DISCUSSION

The analysis of this cohort of critically ill patients showed that ARC was a common finding, which was independently associated with age and absence of diabetes. In addition, the estimated Cl_{Cr} frequently failed to diagnose ARC. The proper identification of ARC required the measurement of a 24-hour Cl_{Cr}. Moreover, the presence of such a condition produced remarkable changes in vancomycin treatment.

Considerable controversies exist regarding the normal upper limit of the glomerular filtration rate. Although normal limits have been defined as 130 and 120mL/min/1.73m^2 for men and women, respectively,[2] values >120-130mL/min/1.73m^2, regardless of gender, have been used for the definition of increased renal clearance.[13,14] A classification system proposed values of Cl_{Cr} >120mL/min/1.73m^2 in the elderly and >150mL/min/1.73m^2 in young adults for the definition of hyperfiltration.[15] In this study, we chose a Cl_{Cr} cutoff of 120mL/min/1.73m^2 for hyperfiltration, taking into account our predominantly old population (61±18 years).

In different groups of critically ill patients with normal plasma creatinine concentrations, several studies have shown that estimated and 24-hour Cl_{Cr} have poor agreement, with the estimated Cl_{Cr} being systematically lower than the 24-hour Cl_{Cr}.[3,16-23] In a group of 86 critically ill patients with increased renal clearance, the sensitivity of estimated Cl_{Cr} for the identification of ARC was only 62%.[3] In a retrospective study of 390 postoperative patients with ARC, 95% limits of agreement between the 24-hour and estimated Cl_{Cr} were wide (-131.7 to 109.3mL/min).[16] Our study showed not only wide limits of agreement (-69 to 82 mL/min) but also low sensitivity of estimated Cl_{Cr} to diagnose ARC (39%). Thus, the correct identification of ARC should rely on measured instead of calculated Cl_{Cr}. The use of measured Cl_{Cr} is also emphasized because of its well-established correlation with drug elimination,[24,25] and the simplicity of urine collection in the ICU.

The incidence of ARC and its determinants has been studied previously. Most of the studies, however, were performed in particular clinical states such as trauma,[26,27] burns[5] and sepsis,[14,26,28] or in small series

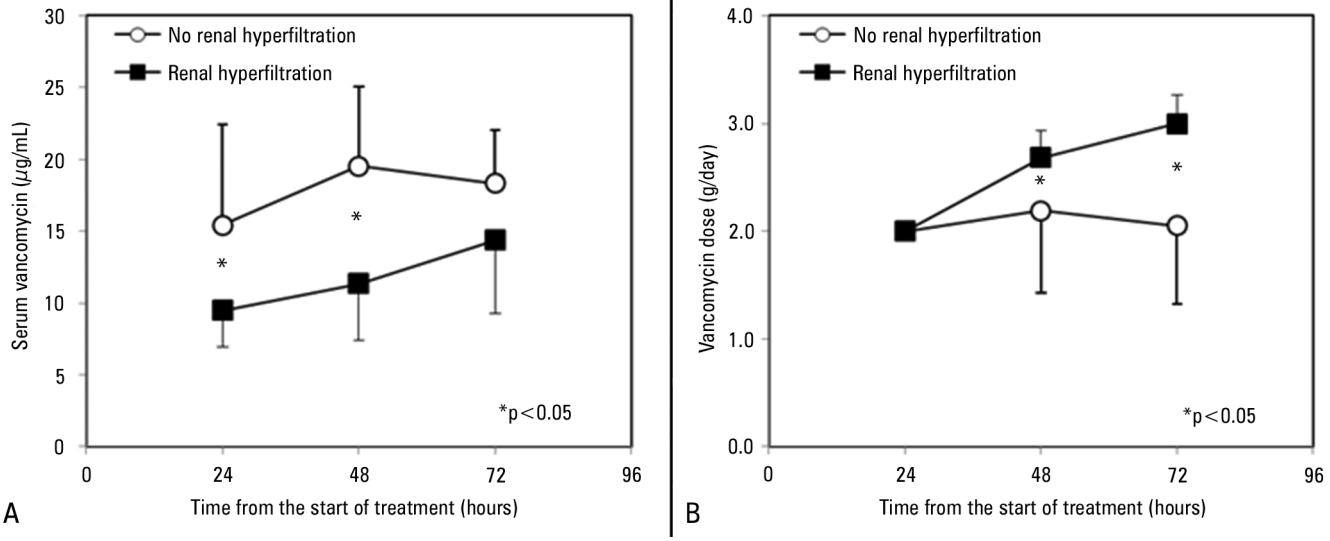

Figure 2 - Panel A) Plasma levels of vancomycin in patients with and without augmented renal clearance. Panel B) Doses of vancomycin in patients with and without augmented renal clearance. Data are shown as the mean±SD. p values are referred to the results of two-way repeated measures of ANOVA.

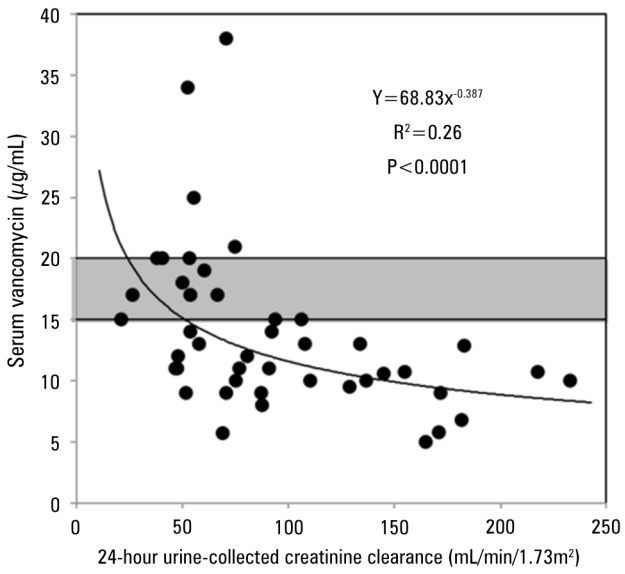

Figure 3 - Relationship between plasma concentrations of vancomycin 24-hour urine-collected creatinine clearance after 24 hours from the beginning of the treatment. Dashed area is the targeted through concentration of vancomycin.

of patients.[5,13,27] In contrast, we studied a large cohort of critically ill patients admitted during a 1-year period to a mixed medical-surgical ICU, of whom 28% had augmented renal clearance on the first day of admission. Similarly, a retrospective analysis of 1317 patients admitted to a surgical ICU found a 24-hour Cl_{Cr} >120mL/min/1.73m^2 in 30% of the cases.[16] Higher incidences were reported in other investigations, but most included young patients. For example, Udy et al. reported increased renal clearance in 58% of septic and trauma patients, with a mean age of 42±17 years.[26] On the other hand, Fuster-Lluch et al. showed that 18% of patients with a median age of 61 years had ARC on ICU admission,[13] while Claus et al. found an incidence of 30% in septic patients, with a median age of 60 years.[28] These figures, quite dissimilar, could be related to the age of the populations studied.

Our results - along with those from other studies - suggest that ARC might be another expression of the response to critical illness, which can be fully manifested only in subjects with an adequate physiologic reserve, namely in young patients without comorbidities.

Our patients with ARC were younger, had trauma or obstetric admissions, and showed less cardiovascular comorbidities and diabetes, compared to those without ARC. Of these factors, only age and absence of diabetes were independently associated with the development of ARC. Young age is the most frequently described independent predictor.[26,28,29] Trauma is often reported as an independent determinant[26,29] and was not identified in our study possibly due to the small number of trauma patients included. Pregnancy is a well-known condition that induces hyperdynamic changes and ARC.[30] During early pregnancy, the glomerular filtration rate measured by inulin clearance increased 32% compared with the pre-pregnant value (from 115±18 to 150±23mL/min/1.73m^2.[31] Although we found increased renal clearance more frequently in patients with obstetric admissions, multivariate analysis showed that this association was related to the younger age of pregnant women.

We found no differences in patients with and without ARC, in terms of volume of fluids infused and the use of norepinephrine. In spite of this, patients with ARC showed higher urinary output and electrolyte excretion, less positive fluid balance, and lower use of furosemide. These findings suggest that the development of ARC was not related to the resuscitation therapy and that the elimination of water and electrolytes was a consequence of ARC.

Patients with ARC had lower plasma concentrations of vancomycin during the first days of treatment, and no patient reached the targeted through level on the first day. This occurred regardless of increasing doses of vancomycin, which after 72 hours from the start of treatment were almost 50% higher than in patients without ARC. Moreover, at this time, mean plasma concentrations were under the lower limit of the suggested levels, implying that most patients with ARC were inappropriately treated. These results confirm the association between ARC and subtherapeutic serum vancomycin levels in critically ill patients.[14] The development of therapeutic failure of antibiotics has repeatedly been associated with the presence of increased Cl_{Cr}.[6-8,28] Because estimated Cl_{Cr} has a poor sensitivity for the identification of ARC, these findings emphasize the need for monitoring both measured Cl_{Cr} and plasma drug concentrations.

This study has some limitations: 1) The measurement of 24-hour Cl_{Cr} is not the gold standard to measure glomerular filtration. The use of inulin or exogenous markers such as iothalamate and EDTA to assess renal function, might produce different results. Albeit tubular creatinine secretion at high filtration rates is improbable,[32] a study in pregnant women with increased glomerular filtration showed that the 24-hour Cl_{Cr} underestimated inulin clearance.[31] 2) ARC was only evaluated on ICU admission. A study showed that 18%

of patients had ARC on admission, but that increased to 30% during the first week of an ICU stay.[13] In addition, the peak in creatinine clearance was found on the 5th day after admission,[4,13] so our data might underestimate the actual incidence of this disorder. 3) We included patients with low APACHE II and SOFA scores, and a large number of postoperative patients. Consequently, our series could not be completely representative of other populations of critically ill patients.

CONCLUSIONS

In this cohort of critically ill patients, 28% had augmented renal clearance on admission to the intensive care unit. Its diagnosis required the measurement of Cl_{Cr} by means of urine collection because estimated Cl_{Cr} showed low sensitivity. Augmented renal clearance mainly developed in young patients without comorbidities, such as diabetes. The most relevant consequence was the lower plasma concentration of vancomycin, despite a higher dosage.

RESUMO

Objetivo: Foi descrito um incremento da depuração renal em alguns grupos de pacientes gravemente enfermos, o qual pode induzir à eliminação de concentrações de fármacos por filtração glomerular aquém do ideal, principalmente no caso de antibióticos. Sua ocorrência e os fatores determinantes têm sido pouco estudados. Nossos objetivos foram determinar a incidência e os fatores associados ao incremento da depuração renal, bem como seus efeitos nas concentrações e na posologia de vancomicina em uma série de pacientes em unidade de terapia intensiva.

Métodos: Estudamos, de forma prospectiva, 363 pacientes admitidos durante 1 ano em uma unidade de terapia intensiva clínico-cirúrgica. Foram excluídos pacientes que tivessem nível de creatinina sérica >1,3mg/dL. A depuração de creatinina foi calculada a partir da coleta de urina de 24 horas. Os pacientes foram agrupados segundo a presença de incremento da depuração renal (depuração de creatinina >120mL/min/1,73m^2), e os possíveis fatores de risco foram analisados por meio de análise bivariada e logística. Em pacientes tratados com vancomicina, foram registradas a posologia e as concentrações plasmáticas.

Resultados: O incremento da depuração renal esteve presente em 103 pacientes (28%), os quais eram mais jovens (48±15 *versus* 65±17 anos; p<0,0001), tinham mais frequentemente admissões obstétricas (16 *versus* 7%; p=0,0006) e por trauma (10 *versus* 3%; p=0,016), e menos comorbidades. Os únicos determinantes independentes para o desenvolvimento de incremento da depuração renal foram idade (OR=0,95; IC95%=0,93-0,96; p<0,0001;) e ausência de diabetes (OR 0,34; IC95% 0,12-0,92; p=0,03). Doze dos 46 pacientes que receberam vancomicina tinham incremento da depuração renal e, apesar das doses elevadas, tinham concentrações plasmáticas de vancomicina mais baixas.

Conclusões: Nessa coorte de pacientes gravemente enfermos, foi frequente o achado de incremento da depuração renal. Idade e ausência de diabetes foram os únicos determinantes independentes. Assim, pacientes jovens e previamente saudáveis podem necessitar de doses mais elevadas de vancomicina.

Descritores: Creatinina; Vancomicina/uso terapêutico; Vancomicina/farmacocinética; Taxa de depuração metabólica; Sepse/quimioterapia

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