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Augmented renal clearance in septic patients and implications for vancomycin optimisation

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ABSTRACT

The aim of this study was to evaluate the effect of augmented renal clearance (ARC) on vancomycin serum concentrations in critically ill patients. This prospective, single-centre, observational, cohort study included 93 consecutive, critically ill septic patients who started treatment that included vancomycin by continuous infusion, admitted over a 2-year period (March 2006 to February 2008). ARC was defined as 24-h creatinine clearance (CL_{Cr}) > 130 mL/min/1.73 m^2. Two groups were analysed: Group A, 56 patients with a $CL_{Cr} \leq 130$ mL/min/1.73 m^2; and Group B, 37 patients with a $CL_{Cr} > 130$ mL/min/1.73 m^2. Vancomycin therapeutic levels were assessed on the first 3 days of treatment (D_1, D_2 and D_3). Serum vancomycin levels on D_1, D_2 and D_3, respectively, were 13.1, 16.6 and 18.6 μmol/L for Group A and 9.7, 11.7 and 13.8 μmol/L for Group B ($P < 0.05$ per day). The correlation between CL_{Cr} and serum vancomycin on D_1 was −0.57 ($P < 0.001$). ARC was strongly associated with subtherapeutic vancomycin serum concentrations on the first 3 days of treatment.

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1. Introduction

Achieving an adequate serum concentration of antibiotic has been a challenge through the years. This challenge is greater when it is related to septic patients admitted to the Intensive Care Unit (ICU). Affected tissues are exposed to great metabolic and haemodynamic variations and these can lead to lower efficacy of antibiotics. The early phase of sepsis is often a hypermetabolic condition leading to increased renal blood flow, glomerular filtration rate (GFR), renal creatinine clearance and clearance of renally eliminated drugs, namely antibiotics [1–4]. This situation is usually ignored by clinicians; however, even though this is underassessed, it should be considered a major cause of treatment failure and emergence of bacterial resistance in critically ill septic patients. Vancomycin has been widely used for many years as a first-choice antibiotic for nosocomial infections due to Gram-positive bacteria. Despite readily available therapeutic drug monitoring (TDM), achieving the correct serum level can be a difficult task, particularly in severely septic patients, even with repeated loading doses and daily increments in perfusion rate, usually with higher doses than normally recommended.

The aim of this study was to evaluate the influence of augmented renal clearance (ARC) on serum vancomycin levels in a population of critical septic patients.

2. Materials and methods

This study was conducted at a 1427-bed teaching hospital belonging to the University of Coimbra (Hospitais da Universidade de Coimbra, Coimbra, Portugal). In total, 93 consecutive, ventilated, adult patients with severe sepsis or septic shock, according to accepted definitions [5], who started empirical or directed treatment that included vancomycin were prospectively enrolled over the 2-year period March 2006 to February 2008. Serum levels were evaluated on the first 3 days of treatment (D_1, D_2 and D_3). Our vancomycin protocol starts with a loading dose, depending on the patient's actual weight, of 1000 mg (body weight ≤70 kg) or 1500 mg (body weight >70 kg) over 1 h, followed by continuous infusion (30 mg/kg/day) irrespective of the patient's 24-h creatinine clearance (CL_{Cr}). Thereafter, daily analysis of serum levels was performed, with 13.8–20.7 μmol/L considered the target level for adequate treatment for Gram-positive microorganisms, including lung infection [6]; if appropriate, dosage adjustment was performed on subsequent days. Vancomycin is stable for slow intravenous administration over a 24-h period [7]. At Hospitais da Universidade de Coimbra, *Staphylococcus aureus* show no resistance to vancomycin [minimum inhibitory concentration (MIC) ≤ 1 μg/mL].

ARC was defined as $CL_{Cr} > 130$ mL/min/1.73 m^2 [8–11]. Body surface area (BSA) was measured, and CL_{Cr} for the 93 patients and adjusted accordingly to create two groups, as follows: Group A (control group) with a $CL_{Cr} \leq 130$ mL/min/1.73 m^2 ($N = 56$ patients); and Group B (study group) with a $CL_{Cr} > 130$ mL/min/1.73 m^2 ($N = 37$ patients). Simplified Acute Physiology Score II and Acute Physiology

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and Chronic Health Evaluation (APACHE) II score were recorded. Diuretic and vasoactive drug use were recorded on the first day of the study. Exclusion criteria for study admission were as follows: (i) renal replacement therapy; (ii) serum creatinine concentration (S_{Cr}) > 115 μmol/L on the first day of the study; (iii) time interval between loading dose and TDM of vancomycin <12 h; and (iv) pregnant women.

2.1. Patient sampling and analytical assay

Single serum and urinary creatinine, single blood urea nitrogen (BUN) and total serum proteins, albumin and vancomycin determinations were determined each morning (7:00–7:30 am) as part of the routine procedure in this unit, as well as the urine collection over a 24-h period.

Serum vancomycin concentrations were measured using a colorimetric turbidimetric immunoassay (PETINIA; Siemens Laboratories, Deerfield, IL). The limit of detection (LOD) was 0.8 μg/mL and the intra-assay coefficient of variation (CV) was between 2.4% and 5.3%. S_{Cr} and urinary creatinine concentration (U_{Cr}) were automatically measured using alkaline picrate methodology. The normal S_{Cr} reference range for adult males and females is 62–115 μmol/L and 53–97 μmol/L, respectively. The LOD was 4.4 μmol/L for S_{Cr} and 119 μmol/L for U_{Cr}; the imprecision of the creatinine assay was <6% total CV for concentrations >88.4 μmol/L and the standard deviation (S.D.) was ≤8.8 μmol/L for concentrations ≤88.4 μmol/L. The BUN was determined automatically using urease methodology. The normal BUN reference range for adult males and females aged >50 years is 3–9.2 mmol/L and 3.5–7.2 mmol/L, respectively, and is 3.2–7.4 mmol/L and 2.5–6.7 mmol/L in the remaining ages. The LOD for BUN was 0.25 mmol/L; the imprecision of the BUN assay was <4.5% total CV. A photometric colour test for quantitative determination of total protein and albumin in human serum and plasma was performed on Hitachi chemistry analysers (Olympus Life and Material Science Europa GmbH, O'Callaghan's Mills, Ireland) according to the manufacturer's recommendations. The normal adult reference intervals are 66–83 g/L and 35–52 g/L for total protein and albumin, respectively.

2.2. Statistical analysis

Continuous variables are expressed as mean or median when applied, together with their dispersion coefficients (S.D. or interquartile range, respectively). Qualitative variables are presented as frequencies and percentages. For subgroup comparison, Student's *t*-test or Mann–Whitney *U*-test were used as indicated. The correlation between continuous variables was established using the Spearman coefficient (*rS*). Multiple regression analyses were performed in order to examine confounding effects or interactions with age and sex. A *P*-value of <0.05 was considered statistically significant.

The results were analysed with the SPSS software package v.13.0 (SPSS Inc., Chicago, IL) and with MedCalc software v.9.3.8 for Windows (MedCalc Software, Mariakerke, Belgium).

2.3. Formulae

CL_{Cr} was calculated according to formula: $CL_{Cr} = (U_{Cr}/S_{Cr}) \times (24\text{-h urinary output}/1440) \times (1.73/BSA)$. The DuBois and DuBois formula was used to calculate BSA: $BSA = 0.007184 \times [\text{height (cm)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$.

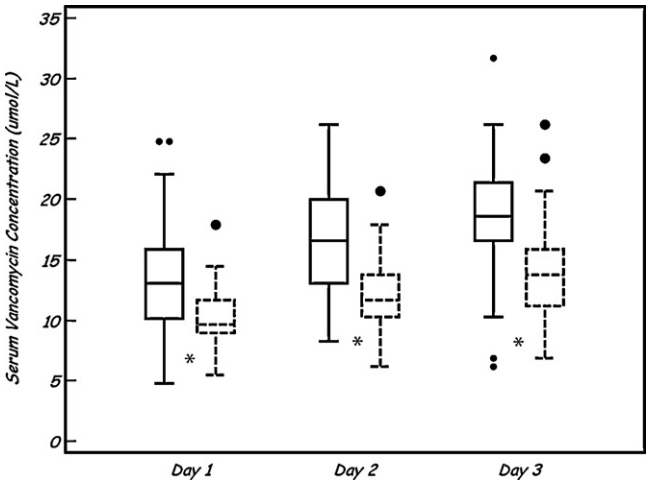

Fig. 1. Box and whisker plots showing the evolution of median (interquartile range) serum vancomycin concentrations on the studied days (Days 1–3) and comparison between Group A [control group without augmented renal clearance (ARC); continuous line] and Group B (study group with ARC; dashed line). * Indicates statistical significance for median differences ($P < 0.01$).

3. Results

The main characteristics and results of the 93 patients are shown in Table 1. In this study, 40% of the patients showed ARC. These patients were significantly younger, less severely ill, with trauma as the leading cause of admission, and with lower BUN on the first day of the study (Table 1).

In Group A, 16 patients (28.6%) were identified with $CL_{Cr} < 60$ mL/min/1.73 m^2. The total amount of vancomycin and the time interval between the loading dose and TDM of vancomycin on D_0 (the day before the first serum level analysis) was equivalent in both groups (Table 2). The serum vancomycin concentration in Group B was significantly lower than in the control group for the 3 days of the study: 13.1 vs. 9.7 μmol/L on D_1, 16.6 vs.11.7 μmol/L on D_2 and 18.6 vs.13.8 μmol/L on D_3 for Groups A and B, respectively (Fig. 1). Only four patients belonging to Group B reached therapeutic levels (>13.8 μmol/L) on D_1 (4/37; 10.8%), 11 patients on D_2 (11/35; 31.4%) and 16 patients on D_3 (16/31; 51.6%). When considering all patients, the correlation (*rS*) between age and serum vancomycin concentration on D_1 was 0.56 ($P < 0.001$) and between CL_{Cr} and D_1 serum vancomycin was −0.57 ($P < 0.001$) (Fig. 2). To assess the independence of CL_{Cr}, multiple regression analysis was performed, which showed that this effect was independent of the age and sex of the patient ($P < 0.01$).

4. Discussion

This study shows that ARC is strongly associated with subtherapeutic serum vancomycin levels in critically ill patients in the early hyperdynamic stage of severe sepsis, even in the presence of TDM. In addition, in patients with normal S_{Cr}, ARC is a frequent condition in the critical care setting (40% of septic patients in this study) and identifies a subgroup of younger and less severe critically ill patients.

Several pathological conditions, such as severe sepsis at early stage, burn injuries, acute leukaemia and severe trauma patients, exhibit hyperdynamic status, hypervolaemia and increased cardiac output, leading to augmented blood flow to major organs [2,12,13]. Subsequently, increased renal blood flow leads to raised glomerular filtration and raised clearance of renally eliminated drugs such as vancomycin. Some authors have described $CL_{Cr} > 120$ mL/min/1.73 m^2 as a frequent condition in recently

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Table 1
Baseline characteristics of the studied population (93 patients) in Group A [control group without augmented renal clearance (ARC)] and Group B (study group with ARC).

	All patients (N = 93)	Group A (N = 56)	Group B (N = 37)	P-value
Males [n (%)]	69 (74.2)	40 (71.4)	29 (78.4)	N/S
Septic shock incidence [n (%)]	30 (32.3)	20 (35.7)	10 (27.0)	N/S
Urine output (mL/day) [mean (S.D.)]	2618 (826)	2459 (740)	2862 (899)	<0.05
Age (years) [median (IQR)]	58 (34–75)	70 (52–79)	41 (32–56)	<0.05
Use of diuretics [n (%)]	60 (64.5)	35 (62.5)	25 (67.6)	N/S
Actual body weight (kg) [median (IQR)]	73.5 (65–85)	74 (61–80)	77 (68.5–88.5)	N/S
APACHE II score [mean (S.D.)]	17.2 (6)	19.1 (6)	14.1 (5.7)	<0.05
SAPS II [mean (S.D.)]	42.2 (14.3)	45.9 (14)	36.3 (12.9)	<0.05
Serum creatinine (μmol/L) [median (IQR)]	70.7 (61.9–79.6)	70.7 (61.9–88.4)	61.9 (53–79.6)	N/S
BUN (μmol/L) [median (IQR)]	8 (5.6–10.4)	8.6 (6.6–11)	5.7 (4.8–8.6)	<0.05
Serum proteins (g/L) [median (IQR)]	53 (48–60)	52 (47–57)	57 (51–62)	<0.05
Serum albumin (g/L) [median (IQR)]	30 (25–34)	27 (24–31)	32 (29–36)	<0.05
CL_{Cr} (mL/min/m^2) [median (IQR)]	109.6 (68.1–152.5)	69.6 (57.8–104.2)	158.9 (140.9–193.6)	<0.05
Admission diagnosis [n (%)]				
Trauma	45 (48.4)	23 (41.1)	22 (59.5)	<0.05
Sepsis	28 (30.1)	22 (39.3)	6 (16.2)	<0.05
Respiratory failure without sepsis	11 (11.8)	8 (14.3)	3 (8.1)	N/S
Post surgery	5 (5.4)	2 (3.6)	3 (8.1)	N/S
Other	4 (4.3)	1 (1.8)	3 (8.1)	N/S

S.D., standard deviation; IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; BUN, blood urea nitrogen; CL_{Cr}, 24-h creatinine clearance; N/S, not significant (at a level of 0.05).

Table 2
Median (interquartile range) vancomycin dose and time interval between loading dose and therapeutic drug monitoring (TDM) of vancomycin on the first treatment day (D_0) for Group A [control group without augmented renal clearance (ARC)] and Group B (study group with ARC).

	Group A	Group B	P-value
Loading dose (g)	1.0 (1.0–1.1)	1.0 (1.0–1.5)	N/S
Perfusion dose (g)	2.0 (1.9–2.4)	2.1 (2.0–2.4)	N/S
Total dose (g)	3.1 (2.9–3.8)	3.4 (3.0–3.9)	N/S
Loading dose/actual weight (mg/kg)	15.4 (12.5–18.2)	14.5 (12.5–18.2)	N/S
Perfusion dose/actual weight (mg/kg)	30 (26.7–34.4)	30 (25.0–32.3)	N/S
Total dose/actual weight (mg/kg)	47.7 (40.0–51.8)	45.4 (38.8–48.6)	N/S
Time interval between loading dose and TDM of vancomycin on D_0 (h)	17 (16–17)	17 (17–18)	N/S

N/S, not significant (at a level of 0.05).

admitted critically ill patients (17.9%), increasing to rates as high as 30% during the first week of admission [11]. Accordingly, serum and tissue subtherapeutic drug levels are the pharmacological consequences, contributing to treatment failure of severe infections. This condition, here defined as ARC, is unappreciated in the critical care setting and is under-reported in the medical literature, and can be a co-factor responsible for inadequate antibiotic prescription despite adequate recommended dosage and respective adjustment to body weight. One of the particularities of the current data was that a group of patients in which renal clearance was actually measured, and not estimated, was studied. A previous study has shown that in critically ill patients exhibiting ARC, estimates of GFR are insensitive in identifying this phenomenon [14].

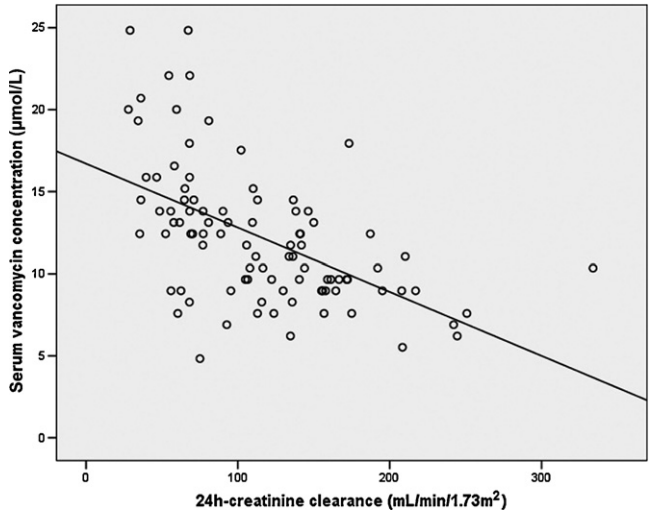

Fig. 2. Linear correlation between 24-h creatinine clearance (CL_{Cr}) and serum vancomycin concentration on Day 1. The serum vancomycin concentration displayed a significant direct correlation with CL_{Cr} in 93 septic critically ill patients (rS = –0.57; P < 0.01).

Vancomycin is a hydrophilic drug with predominantly renal excretion (80–90%), whose clearance correlates with CL_{Cr} [15,16]. It shows time-dependent activity that, in turn, is linked to the ratio of the 24-h area under the concentration–time curve (AUC_{24}) to MIC. As shown in Fig. 1, the serum vancomycin concentration in Group B just reached, on average, therapeutic levels on D3 (13.8 μmol/L). Actually, only 52% of patients (16/31) reached minimal therapeutic serum levels, meaning that approximately one-half of the patients have not yet started optimal treatment of infection on D3, in other words only 72 h after the vancomycin loading dose. These results are in agreement with another recent study in which the authors found that in critically ill patients a higher dose of vancomycin in continuous infusion than usual is needed, following an adequate loading dose, to achieve a target plateau concentration of 17.3 μmol/L (25 μg/mL) [17].

Patients in both groups, on average, were treated with an equivalent total amount of vancomycin (loading plus maintenance dose) during the 24 h of D_0 (Table 2). A very high rate of subtherapeutic serum vancomycin concentration was observed on D_1, mostly in Group B (89%) but also in Group A (53%). This last result was unexpected since Group A had 28.6% of patients (16/56) with CL_{Cr} < 60 mL/min/1.73 m^2. It is possible that, in these patients without ARC, other factors such as hypoalbuminaemia and increased volume of distribution (V_d), could contribute to this low therapeutic level on D_1. Serum albumin, a major determinant of V_d, was

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significantly higher in patients with ARC (Group B), an event that is not surprising since this group was younger, less severely ill and with a higher potential physiological reserve. Moreover, vancomycin is not a highly albumin-bound drug (30–55%) so it should not greatly influence vancomycin availability; however, even for hydrophilic antibiotics with low albumin binding, increased V_d has been described [18,19].

Although we have analysed a considerable number of patients ($n = 93$), the main limitation of the present study lies in the fact that it is a single-centre study, reflecting the case mix of our ICU, namely with a significant trauma population. Furthermore, the CL_{Cr} measurement is laborious and this factor could be a bias for imperfect urine collection, thus leading to clearance miscalculations. Finally, V_d was not assessed in this study, thus the discussion around this issue is merely speculative.

In conclusion, amongst critically ill patients with normal S_{Cr}, ARC is strongly associated with subtherapeutic serum vancomycin levels and this study clearly shows the need to use a more aggressive initial loading dose as well as TDM in these particular patients. ARC appears to be a relatively frequent occurrence in this setting, namely in young males with trauma and less severe disease.

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Competing interests: None declared.

Ethical approval: This study was approved by the Institutional Review Board of the Committee of the Innovation and Development Unit, Coimbra University Hospital (Coimbra, Portugal) (Project Approval No. 42/IDU/10/D).

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