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Relationship between vancomycin trough concentration and 24-h area under the curve concentration in Tunisian patients

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The 24-h area under the curve concentration ($AUC_{24\ h}$) is associated with better clinical and bacteriological response to vancomycin in patients with methicillin-resistant *Staphylococcus aureus* who achieve the target $AUC_{24\ h}$ between 400 and 700 mg×h/L. Recent consensus recommends maintaining trough concentrations between 15 and 20 mg/mL as a convenient target to reach an AUC/minimum inhibitory concentration (MIC) ≥ 400. The aim of this study was to determine the correlation between a calculated $AUC_{24\ h}$ and a measured trough vancomycin concentration (C_0). We conducted a retrospective observational study. Hospitalized patients prescribed vancomycin for a presumed or documented invasive staphylococcal infections were evaluated. A formula based on the relationship between dose, vancomycin clearance and creatinine clearance was used to determine each patient's $AUC_{24\ h}$. 161 patients were included in the study. Median age was 34 years. The mean daily dose of vancomycin was 28 mg/kg/day. The median vancomycin C_0 was 12.2 mg/mL, 17.3% were in the therapeutic range. The median AUC was 246.84 mg×h/L, only 8% achieved the target $AUC_{24\ h}$ between 400 and 700 mg×h/L. Of these, 3 patients had C_0 between 15 and 20 mg/mL and 9 patients had C_0> 20 mg/mL. A poor correlation was found between C_0 and $AUC_{24\ h}$ = 0.37; r^2 = 0.14; p<0.0001. In conclusion, vancomycin C_0 correlated poorly with AUC_{24}/MIC targets. C_0 seems to underestimate $AUC_{24\ h}$. So, a patient specific AUC_{24}/MIC may serve to predict efficacy while C_0 can be used as indicators of possible nephrotoxicity and development of resistance.

Key words: Vancomycin, area under the curve (AUC), trough concentration, minimum inhibitory concentration, therapeutic drug monitoring.

INTRODUCTION

Vancomycin is a tricyclic glycopeptide antibiotic (Hale et al., 2017) widely used in clinical care units. It is the drug of choice for serious Gram positive infections (Ghosh et al., 2014). A serum trough concentration between 10 and

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20 mg/mL was associated with a successful treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) (Thompson et al., 1993; Meng et al., 2019). In fact, serum vancomycin trough concentrations are suggested as a surrogate for achieving a ratio of the area under the concentration curve (AUC) to minimum inhibitory concentration (MIC) of ≥400 for an organism with MIC ≤1 mg/mL (Liu et al., 2011).

Numerous studies have found that maintaining an AUC/MIC ≥ 400 predicted time-related clinical and bacteriogical success for patients with infections caused by MRSA (Thompson et al., 1993; Liu et al., 2011). Because of the emergence of bacterial resistance, consensus guidelines issued by the infectious diseases society of America in 2009, recommend maintaining trough concentrations between 15 and 20 mg/mL as a convenient target to reach an AUC/MIC≥400 (Thompson et al., 1993; Fowler et al., 2005) in severe infections. However, recently, it was reported that vancomycin trough concentration does not accurately predict AUC. Additionally, AUC was underestimated by 23%, and this may lead to over exposure and subsequent nephrotoxicity (Neely et al., 2014). So, this study aimed to determine the correlation between measured vancomycin trough concentration and a calculated AUC/MIC ratio in Tunisian patients treated by vancomycin.

METHODS

Population and samples

This study was conducted among patients treated with vancomycin for a suspected or proven Gram-positive infection and addressed to the department of Clinical Pharmacology of the National Pharmacovigilance Centre for therapeutic drug monitoring (TDM) of vancomycin during the period from 24 January 2010 to 13 April 2021. It included 161 samples from 161 patients receiving a slow intravenous infusion of vancomycin.

Blood samples were taken just before the next drug intake (trough concentration C_0). The samples were collected in EDTA tubes and monitored by the chemiluminescent microparticle immunoassay method (CMIA) on Architect 8000. The CMIA method is linear from 7.69 to 96.97 µg/mL range (r= 0.99). Detection (LOD) and quantification limits (LOQ) were 0.42 and 3 µg/mL, respectively.

Data acquisition

A standardized form was used to collect data including age, sex, indication and dose of vancomycin, weight, creatinine clearance, medication administration data and serum concentration data.

We excluded all insufficient data (lack of dose, weight or creatinine) and data with non-valid concentrations (C_0 under the limit of detection, samples taken after the vancomycin administration).

Calculations and definitions

AUC over 24 h was calculated using the Rodvold method (Biagi et al., 2019). The formula was based on a relationship between total body clearance of vancomycin, patient specific creatinine clearance and total daily dose of vancomycin:

$$AUC = dose/[(CrCl \times 0.79) + 15.7] \cdot 0.06$$

Creatinine clearance was estimated with Cockcroft-Gault equation (mL/min).

Statistical analysis

The correlation between through vancomycin concentrations and $AUC_{24\ h}$ was analyzed through a Pearson correlation coefficient and a regression model. Statistical analyses were performed by using GraphPad® and Microsoft Excel®.

RESULTS

One hundred sixty-one trough vancomycin concentrations derived from 161 patients were included in the study. The samples were analyzed with CMIA method. The linear range was from 7.69 to 96.97 µg/mL (r= 0.99) and the detection (LOD) and quantification limits (LOQ) were 0.42 and 3 µg/mL, respectively. Demographic data and vancomycin dosing characteristics for the population are shown in Table 1.

The median C_0 was 12.2 mg/mL (range: 1.64-48.77 mg/mL); the median AUC over 24 h was 246.84 mg×h/L (range: 41.495-783.39 mg×h/L) with only 7.5% achieving $AUC_{24\ h}$ values ranging from interval 400 to 700 mg×h/L. Of these, 3 patients had C_0 between 15 and 20 mg/mL and 9 patients had C_0> 20 mg/mL. Only 3 patients (1.9%) had a supratherapeutic $AUC_{24\ h}$ value (AUC_{24}>700) with corresponding vancomycin C_0 above 20 mg/L.

Those with an infratherapeutic $AUC_{24\ h}$ value (145 patients, 90.1%) had a median corresponding C_0 of 11.22 mg/L with 94 (58%) less than 15 mg/mL, 25 (15%) between 15-20 mg/mL and 26 (16%) above 20 mg/mL.

There was a little positive correlation found between AUC/MIC and trough vancomycin concentrations (r = 0.37; r^2 = 0.14; p<0.0001) (Figure 1).

DISCUSSION

In this retrospective study, we sought a limited correlation between plasma vancomycin trough concentration and achieving a calculated AUC/MIC ratio ≥400 when trough concentrations are above 15 mg/mL. Current published data indicate that dosing based on vancomycin trough concentrations underestimate AUC by 23%(7).

In the present study, we found that 89% (25 of 28) of patients with vancomycin trough concentration between 15 and 20 mg/mL did not achieve the pharmacodynamic target of AUC/MIC ≥400. Otherwise, 9 patients of 12 with vancomycin trough concentration above 20 mg/L achieve the pharmacodynamic target of AUC/MIC ≥400.

Table 1. Patient and therapy characteristics.

Characteristic	Value
Age, year; median [min-max]	34 [16-78]
Male gender; n (%)	116 (72.04)
Weight, Kg; median [min-max]	68.5 [30-120]
Serum creatinine, µmol/L; median [min-max]	61.88 [35.36-97.24]
Creatinine clearance, mL/min; median [min-max]	142.068 [72.6-969.9]
Therapy characteristics	
Daily dose of vancomycin; mg/kg/day; median [min-max]	28.84 [11-75]
Frequency of administration of vancomycin; n (%)	
Every 6 h	24 (14.9)
Every 8 h	84 (52.17)
Every 12 h	53 (32.91)
AUC, mg×h/L ; median; [min-max]	246.84 [41.49-783.3]
Trough concentration, mg/mL; median [min-max]	12.2 [1.64-48.77]
C_0<15 mg/L; n (%)	95 (59)
15<C_0<20 mg/L; n (%)	28 (17.39)
C_0>20 mg/L; n (%)	38 (23.6)

Source: Authors 2023

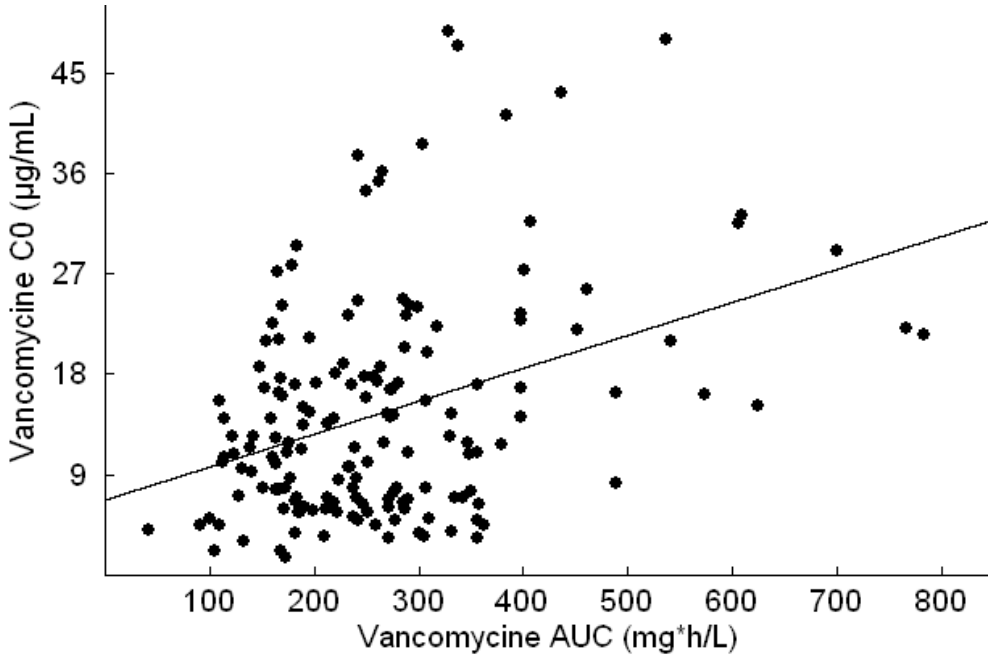

Figure 1. Fit plot for AUC and trough vancomycin concentrations of all 161 participants. Each black dot represents 1 participant. The black line is on the fit line.
Source: Authors 2023

Previously, in a study of Hale et al. (2017), 53.4% of patients with vancomycin trough concentrations between 15 and 20 mg/mL did not reach an AUC/MIC ≥400(1). Similar results were reported by a retrospective cohort

study of Ghosh et al. (2014). This seems to contradict consensus recommendations for therapeutic drug monitoring of vancomycin which suggest a minimum trough concentration of 15 mg/mL to reach target AUC/MIC (Thompson et al., 1993; Meng et al., 2019).

It is clear from the present study that optimizing individual patient vancomycin exposure requires monitoring of both $AUC_{24\ h}$ and MIC values. So, it seems that using trough concentration to adjust vancomycin dose does not allow achieving the recommended targets and has a consequence the possible emergence of vancomycin resistance with subtherapeutic concentration and increased the risk of nephrotoxicity with increasing drug exposure.

However, the present study has some limitations. First, this was a retrospective design that did not assess clinical outcomes. Additionally, we calculated AUC using the Rodvold method which relates patient specific creatinine clearance to total body clearance of vancomycin (Biagi et al., 2019). This method may slightly underestimate the true AUC. In another hand, this method is characterized by its rapidity and practicality. It can be especially used to optimize empiric dosing in patients with suspected *S. aureus* infections.

Another potential limitation was that we supposed that MIC values of all cases were 1 mg/L because of insufficient information accompanying the prescriptions. Clinicians should be mindful of the importance of MIC results on the final AUC_{24}/MIC (Meng et al., 2019; Liu et al., 2011; Sakoulas et al., 2004). For example, double the AUC might have been achieved in those with *staphylococcus aureus* with a MIC of 0.5 mg/L compared to 1 mg/L, such as MICs of 2 mg/L requires seeking an alternative therapy with less renal toxicity (Biagi et al., 2019).

In conclusion, vancomycin steady state trough concentrations correlated poorly with AUC_{24}/MIC targets. In order to improve therapeutic drug monitoring of vancomycin, a patient specific AUC_{24}/MIC may serve to predict efficacy while serum trough concentrations can be used as indicators of possible nephrotoxicity and development of resistance.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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