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# **A higher dose of vancomycin in continuous infusion is needed in critically ill patients**

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## ABSTRACT

Compared with intermittent infusion, continuous infusion of vancomycin is cheaper and logistically more convenient, achieves target concentrations faster, results in less variability in serum vancomycin concentrations, requires less therapeutic drug monitoring and causes less nephrotoxicity. Given that critically ill patients may develop very large volumes of distribution as well as supranormal drug clearance, in this study it was shown, despite the limited number of patients studied, that to achieve a target plateau concentration of 25 mg/L a daily dose of 3000 mg of vancomycin in continuous infusion is needed following an appropriate loading dose.

## 1. Introduction

Vancomycin exhibits time-dependent bactericidal activity against most Gram-positive bacteria [1]. However, experimental models in neutropenic mice have shown some concentration-dependent activity [maximum drug concentration/minimum inhibitory concentration ratio ( $C_{\max}/\text{MIC}$ )], with advantages also evident when the area under the concentration–time curve (AUC) to MIC ratio (AUC/MIC) is maximised [2]. Therefore, the question remains whether intermittent dosing or continuous infusion is preferred.

Compared with intermittent infusion, continuous infusion of vancomycin is cheaper and logistically more convenient, achieves target concentrations faster, results in less variability in serum concentrations and requires less therapeutic drug monitoring (TDM) [3]. Furthermore, in patients with normal renal function, vancomycin in continuous infusion is associated with a slower onset of nephrotoxicity [4].

The Intensive Care Unit at GZA St Vincentius Hospital (Antwerp, Belgium) has been administering the standard vancomycin dosage (2000 mg intravenous daily, adjusted to the patient's renal function if necessary) by continuous infusion. The aim of this study was, as previously described by Pea et al. [5], to assess retrospectively the correlation between vancomycin clearance ( $\text{CL}_v$ ) and creatinine clearance ( $\text{CL}_{\text{Cr}}$ ) in a cohort of critically ill patients in order to construct a dosing nomogram to obtain a target vancomycin steady-state concentration ( $C_{\text{ss}}$ ) of 25 mg/L for use in daily clinical practice.

## 2. Methods and materials

All critically ill patients ( $n = 20$ ) who were treated with vancomycin by continuous infusion between April 2009 and April 2010 were included in this study. An initial loading dose of 1 g was administered over 1 h, with continuous infusion starting immediately afterwards. The vancomycin concentration was determined by competitive inhibition enzyme-linked immunosorbent assay (ELISA) performed on a VITROS Fusion System (Ortho-Clinical Diagnostics, Beerse, Belgium). Knowing that (i) vancomycin follows a first-order elimination, (ii) the serum half-life of vancomycin is 4–5 h and (iii) steady state is reached at five times the serum half-life, it was concluded that in patients with normal renal function a steady-state concentration of vancomycin would be reached at 24 h after the start of therapy. As the half-life of vancomycin is increased when renal function is diminished, a steady-state concentration of vancomycin was supposed to be reached at 48 h in patients with  $CL_{Cr} < 60$  mL/min [6]. Therefore, TDM data for vancomycin on Day 2 for patients with normal renal function and on Day 3 for patients with  $CL_{Cr} < 60$  mL/min were used to estimate  $CL_v$  by means of the following formula:  $CL_v$  (L/h) = infusion rate (mg/h)/ $C_{ss}$  (mg/L). As vancomycin is mainly eliminated by glomerular filtration, the correlation between  $CL_v$  and  $CL_{Cr}$  was assessed by linear regression analysis.  $CL_{Cr}$  was estimated by means of the Cockcroft–Gault formula. In the patients studied, mean  $CL_{Cr}$  was 95 mL/min, and in 7/20 patients (35%) the  $CL_{Cr}$  was  $<60$  mL/min. The resulting  $CL_v$  was used to create a dosing nomogram for critically ill patients receiving vancomycin by continuous infusion to a target  $C_{ss}$  of 25 mg/L.

### 3. Results

Fig. 1 shows the relationship between  $CL_v$  and  $CL_{Cr}$ , which was highly significant  $\{[CL_v \text{ (L/h)} = 0.0261 \times CL_{Cr} \text{ (mL/min)} + 1.78]; r = 0.83; P < 0.001\}$ . From this correlation and using the formula  $CL_v \text{ (L/h)} = \text{infusion rate (mg/h)} / C_{ss} \text{ (mg/L)}$ , the following formula was used to calculate the rate of vancomycin continuous infusion required, as a function of  $CL_{Cr}$ , to achieve the appropriate  $C_{ss}$ : infusion rate (g/24 h) =  $[0.0261 \times CL_{Cr} \text{ (mL/min)} + 1.78] \times \text{target } C_{ss} \times (24/1000)$ .

Fig. 2 shows the nomogram based on different  $CL_{Cr}$  estimates for calculation of the daily vancomycin dosage by continuous infusion to a target  $C_{ss}$  of 25 mg/L. These results show that in patients with normal renal function ( $CL_{Cr} = 120 \text{ mL/min}$ ), a daily dose of 3000 mg vancomycin in continuous infusion (following a loading dose of 1000 mg) is needed to achieve the target  $C_{ss}$  of 25 mg/L on Day 2.

### 4. Discussion

Vancomycin exhibits time-dependent antibacterial activity and no in vitro concentration-dependent killing effect against staphylococci [7]. Given these pharmacodynamic characteristics, one would predict that the time that the vancomycin serum level exceeds the MIC would be the pharmacodynamic parameter that most strongly correlates with efficacy [5].

In the era of increasing resistance among micro-organisms, optimal dosage of vancomycin has become extremely important. Development of staphylococcal resistance to vancomycin has been associated with prolonged exposure to low

serum concentrations of the drug [8]. Furthermore, a significantly higher mortality rate is associated with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia due to strains with vancomycin MICs  $>1$  mg/L [9]. Therefore, large intermittent daily doses with the intent of achieving a trough concentration ( $C_{\min}$ ) of 15–20 mg/L in all patients may be used, but the unacceptably increased risk of nephrotoxicity recently documented in patients with very high  $C_{\min}$  during intermittent administration of high-dose vancomycin argues against this choice [10]. Accordingly, application of continuous infusion with a target plateau concentration of 20–25 mg/L may be helpful in maximising the pharmacodynamics of vancomycin against staphylococcal infections while avoiding the risk of nephrotoxicity. Continuous infusion of vancomycin to obtain plateau concentrations of 20–25 mg/L is safe and shows good clinical efficacy [3]. The efficacy of vancomycin is optimal when the 24-h AUC/MIC ratio is  $\geq 400$  [11]. To achieve this target for *S. aureus* strains with MICs of 1 mg/L, a continuous serum concentration of 20 mg/L is needed [11]. However, as a tendency towards increasing vancomycin MICs ( $\geq 1$  mg/L) in *S. aureus* clinical isolates is already being reported, a plateau concentration of vancomycin of 25 mg/L seems more appropriate [12]. Moreover, the pharmacokinetics of vancomycin can be significantly altered in critically ill patients. As an increased volume of distribution and/or increased drug clearance can result in lower vancomycin concentrations, administration of vancomycin by continuous infusion may enable more consistent attainment of target concentrations [7]. The present results show that, in critically ill patients with normal renal function, a daily dose of 3000 mg of vancomycin in continuous infusion (following a loading dose) is required to achieve a plateau concentration of 25 mg/L. Only recently, Revilla et al. [13] found, based on a



population model using Monte Carlo simulations, that a dose of 3 g vancomycin was needed for an adequate response in patients with *S. aureus* infections.

Using the target of 25 mg/L, the risk of nephrotoxicity is rather limited. In a multivariate analysis, Ingram et al. [14] found that nephrotoxicity was associated with vancomycin concentrations of  $\geq 28$  mg/L. The same authors recently reported that in adult outpatients with normal renal function, vancomycin by continuous infusion was associated with a slower onset of nephrotoxicity [4]. Furthermore, Hutschala et al. [15] showed a tendency for less nephrotoxicity with continuous infusion compared with intermittent infusion of vancomycin.

In conclusion, these results show that in critically ill patients, following a loading dose of 1000 mg, a daily dose of 3000 mg of vancomycin in continuous infusion is needed to achieve target serum concentrations of 25 mg/L. In patients with decreased renal function, a nomogram based on the Cockcroft–Gault formula can be used for dose adjustment.

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### **Competing interests**

None declared.

### **Ethical approval**

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**Fig. 1.** Relationship between vancomycin clearance ( $CL_v$ ) and creatinine clearance ( $CL_{Cr}$ ):  $CL_v$  (L/h) =  $0.0261 \times CL_{Cr}$  (mL/min) + 1.78 ( $r = 0.83$ ).

**Fig. 2.** Nomogram based on creatinine clearance ( $CL_{Cr}$ ) estimates for calculation of vancomycin daily doses administered by continuous infusion to target a vancomycin steady-state concentration ( $C_{ss}$ ) of 25 mg/L.



