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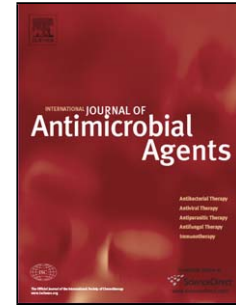
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Clearance of vancomycin during continuous infusion in Intensive Care Unit patients: correlation with measured and estimated creatinine clearance and serum cystatin C

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ABSTRACT

Vancomycin (VAN) dosing requires adjustment to renal function, which is often estimated using the Cockcroft–Gault formula; however, its precision is poor in Intensive Care Unit (ICU) patients. VAN clearance (CL_{Van}) during continuous infusion was prospectively determined in 25 ICU patients [14 male, 11 female; age range 31–82 years; body mass index (BMI) 16.5–41.5 kg/m²; Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission 8–36; creatinine clearance 25–195 mL/min) and its correlation with measured creatinine clearance (CL_{Crea}), estimated creatinine clearance using the Cockcroft–Gault formula (CL_{CG}) and estimated glomerular filtration rate according to Hoek’s formula based on serum cystatin C (GFR_{Hoek}) was investigated. The correlation between CL_{Van} and CL_{Crea} was very good ($r^2 = 0.88$), but it was rather poor with CL_{CG} ($r^2 = 0.37$) and was acceptable with GFR_{Hoek} ($r^2 = 0.70$). For VAN dose adjustments in ICU patients, determination of cystatin C may be an interesting and practical alternative to measured CL_{Crea} , whereas the Cockcroft–Gault formula should be used with caution.

1. Introduction

Vancomycin (VAN) is still the standard treatment for infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), despite the introduction of some alternative agents [1,2]. However, the narrow therapeutic range and a trend towards higher minimum inhibitory concentrations (MICs) make precise dosing of VAN preferable for successful treatment and, for this purpose, sound population-specific pharmacokinetic data are required [3].

VAN is predominantly eliminated via the kidney and the maintenance dose is mainly determined by the glomerular filtration rate (GFR) [4]. The GFR can be determined by various methods, the validity of which are typically proportional to effort. Whereas clearance of exogenous substances such as inulin is the suggested gold standard, measured creatinine clearance can be considered as the clinical reference standard. Assuming constant and predictable production of creatinine, its clearance can be estimated from serum creatinine alone, e.g. using the popular Cockcroft–Gault formula [5]. By analogy, serum cystatin C has been established as an indicator of GFR [6].

Surprisingly, there are only few pharmacokinetic studies on VAN in Intensive Care Unit (ICU) patients without renal replacement therapy. Only one study used a classic prospective pharmacokinetic design [7], whereas three other studies retrospectively analysed data from routine therapeutic drug monitoring (TDM) [8–10]. These studies exclusively used estimations based on serum creatinine as a measure of renal function, although the underlying assumptions are particularly questionable in critically ill patients [11–16]. Consequently, in these studies a large part of the

variance in VAN clearance remains unaccounted for. It is unclear whether this reflects unknown physiological changes during critical illness or the shortcomings of the applied methods.

Although clinical superiority in terms of outcome has not been demonstrated, there is substantial theoretical support for continuous infusion of VAN [17]. In the surgical ICU at Charité University Hospital, Campus Benjamin Franklin (Berlin, Germany), continuous infusion is applied as the standard administration form because it simplifies interpretation of TDM and dose adjustments. As an ancillary effect, continuous infusion permits easy determination of drug clearance. At steady state, determination of a single plasma concentration would suffice for calculation of clearance.

The aim of this study was to determine VAN clearance (CL_{Van}) in ICU patients during continuous infusion and to investigate its relationships with measured creatinine clearance (CL_{Crea}), estimated creatinine clearance using the Cockcroft–Gault formula (CL_{CG}) and estimated GFR according to Hoek's formula based on serum cystatin C (GFR_{Hoek}), as a basis for dosing recommendations.

2. Patients and methods

2.1. Study design and patients

This prospective, single-centre study was approved by the Institutional Ethics Committee of Charité University Hospital. Adult patients in the 22-bed surgical ICU who received treatment with VAN continuous infusion were enrolled. Patients

undergoing renal replacement therapy were excluded. Written informed consent was obtained from either the patient or their legal representative.

2.2. Vancomycin dosage and therapeutic drug monitoring

The attending physician started VAN treatment when infection by a susceptible pathogen was proven or suspected. According to the internal protocol, a loading dose was administered as a 1-h infusion, followed by continuous infusion of VAN. The initial infusion rate was chosen according to the estimated creatinine clearance. Daily at 05:00h, TDM was performed and the infusion rate was adjusted to a target concentration between 20 mg/L and 25 mg/L.

2.3. Pharmacokinetic calculations

As soon as routine TDM showed the VAN serum concentration to be within the desired range and the infusion rate had not been changed for more than 24 h, blood was sampled from arterial catheters at 11:00h, 17:00h, 23:00h and 05:00h. Urine was collected quantitatively in three 6-h fractions from 11:00h to 05:00h. VAN and creatinine concentrations were determined in all serum specimens and, owing to budgetary restrictions, cystatin C was determined only in the first and last specimens. Urine specimens were analysed for creatinine.

Clearance of VAN (CL_{Van}) and creatinine clearance (CL_{Crea}) were calculated as follows:

$CL_{\text{Van}} = \text{infusion rate of VAN} / \text{serum concentration of VAN}$

$CL_{\text{Crea}} = (\text{urine volume} \times \text{urine concentration of creatinine}) / (\text{collection time} \times \text{serum concentration of creatinine})$

Creatinine clearance based on serum creatinine (CL_{CG}) was estimated using the Cockcroft–Gault formula [5]:

$CL_{\text{CG}} \text{ (mL/min)} = [140 - \text{age (years)}] \times \text{weight (kg)} / [72 \times \text{serum creatinine (mg/dL)}] \times 0.85 \text{ for women}$

GFR based on serum cystatin C was estimated by the Hoek formula (GFR_{Hoek}) [18] and the Du Bois formula for body surface area (BSA) [19]:

$GFR_{\text{Hoek}} = [80.35 / \text{serum cystatin C (mg/L)} - 4.32] \text{ mL/min} / 1.73 \text{ m}^2 \times \text{BSA}$

$\text{BSA (m}^2\text{)} = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}$

2.4. Analysis of vancomycin, creatinine and cystatin C

Blood samples were allowed to clot for 30 min, centrifuged and stored at $-20\text{ }^{\circ}\text{C}$.

Urine samples were frozen at $-20\text{ }^{\circ}\text{C}$ without prior treatment. Routine TDM was performed in the hospital's central laboratory (Patients 1 to 13, VANC2, Roche Diagnostics, Mannheim, Germany; and Patients 14 to 25, QMS[®] Vancomycin, Thermo Fisher Scientific, Dreieich, Germany). Serum concentrations of VAN for pharmacokinetic calculations were assayed by high-performance liquid

chromatography (HPLC) with photometric detection at 240 nm as previously described [20]. A reversed-phase column (Gemini-NX C18, 3 μ m, internal diameter 15 \times 0.46 cm; Phenomenex, Aschaffenburg, Germany) was used for separation with an eluent composed of 1000 mL of 50 mM sodium dihydrogen phosphate and 100 mL of acetonitrile. The pH was adjusted to 3.9 with *o*-phosphoric acid. Interference by concomitant medication in a few patients could be avoided by adjusting the pH between 3.9 and 3.1, as the retention time of VAN is sensitive to pH. Based on spiked quality control samples, intra- and inter-assay imprecision as well as bias were <5%.

Concentrations of creatinine were determined enzymatically using an ADVIA Chemistry System (ECRE 2; Siemens Healthcare Diagnostics, Eschborn, Germany). Concentrations of cystatin C were determined using a BNTM II Nephelometer (Siemens Healthcare Diagnostics).

2.5. Statistical analysis

SPSS 17 for Mac OS X (SPSS Inc., Chicago, IL) was used for statistical analysis. Parametric linear regression was used to evaluate correlations between parameters. Two-sided α errors <0.05 were considered statistically significant and were reported as *P*-values. Data are presented as median (range) or mean (95% confidence interval), as appropriate.

3. Results

A total of 25 patients (14 male, 11 female) were enrolled in the study (Table 1). Most commonly, sampling was performed around Day 5 (range, Day 2–15) of treatment with VAN. In one patient, only one 6-h interval (two serum samples and one urine fraction) was available because VAN treatment was terminated. The concentrations were sufficiently constant to assume steady-state conditions in 24 patients, whereas in 1 patient a continuous decline of 32% over 18 h was observed, probably due to acute arterial hypertension with enhanced glomerular filtration. In this patient, only the last concentration, which is closest to steady-state, was used to calculate CL_{VAN} .

The study population exhibited a wide range of renal function, with a median CL_{Crea} of 106 mL/min (range 25–195 mL/min), providing an excellent basis to assess the relationship between CL_{VAN} and renal function. Fig. 1 depicts the relationships between CL_{VAN} with CL_{Crea} , CL_{CG} and GFR_{Hoek} . The respective regression equations and coefficients of determination are shown in Table 2.

4. Discussion

The present study compares measured creatinine clearance (CL_{Crea}), creatinine clearance estimated by the Cockcroft–Gault formula from serum creatinine (CL_{CG}) and GFR estimated by the Hoek formula from serum cystatin C (GFR_{Hoek}) as determinants of CL_{VAN} in ICU patients.

As could be expected, CL_{Crea} showed the closest correlation with CL_{VAN} with a residual error ($1-r^2$) of only ca. 12%, which includes measurement errors and further

undetected covariates. Apart from analytical errors, pharmacokinetic calculations assume constant physiological conditions throughout the study period, which is probably never true in ICU patients. Thus, it seems unlikely that further research would identify additional relevant covariates of CL_{Van} in comparable populations.

In principle, estimation of GFR based on serum concentrations of endogenous markers alone works like the calculation of drug clearance during continuous infusion, as applied in this study for VAN:

Clearance = infusion or production rate/serum concentration

For ideal markers, which undergo exclusive elimination by free glomerular filtration, clearance would be equal to the GFR, whilst restricted filtration, secretion, re-absorption or non-renal clearance may require corrective factors. The Cockcroft–Gault formula estimates creatinine production from age, weight and sex, whereas the Hoek formula assumes cystatin C production to be proportional to BSA. Catabolism, immobilisation and other disturbances of homeostasis negatively affect the precision of these formulas in ICU patients, as has been documented by a number of previous studies [11–16].

In a recent study in Japanese non-ICU patients, GFR_{Hoek} correlated very well with CL_{Van} ($r^2 = 0.84$) [21]. As outlined above, it is not surprising that the formula performs worse in the ICU patients in the current study, but the correlation ($r^2 = 0.70$) seems acceptable. We would like to emphasise that the Hoek formula estimates GFR, which

is systematically lower than creatinine clearance owing to some tubular secretion of creatinine.

Regarding CL_{CG} , although the correlation is statistically highly significant, its value in predicting CL_{Van} in ICU patients seems doubtful. Other studies in ICU patients reported correlations with r^2 between 0.43 and 0.56 [7–10], which is somewhat better than in the data here ($r^2 = 0.37$). However, in one study patients who had been in hospital for more than 14 days were excluded [8], and in another study the Cockcroft–Gault formula was modified by truncating values above 120 mL/min [10]. It should be kept in mind that exact values throughout all the pathophysiological range are required for reliable drug dosing, not just the discrimination of normal from abnormal renal function.

Of course, using the Cockcroft–Gault formula is probably the easiest and least expensive way to obtain an estimate of renal function. However, collecting urine in ICU patients is typically performed anyway for calculating fluid balances and seems a small additional effort, which is rewarded by a substantial gain in precision. Several studies suggest that short collection periods of 1–2 h are sufficient for accurate measurements [11,12,22,23]. We therefore recommend the use of measured CL_{Crea} for prediction of CL_{Van} in ICU patients.

Our data can be used as a basis to predict dosing requirements. Current recommendations suggest an area under the concentration–time curve from 0–24 h (AUC_{24h})/MIC of 400 h as the relevant pharmacokinetic/pharmacodynamic target [3], which corresponds to a mean serum concentration (C_{mean}) of 16.7 mg/L for an MIC of

1.0 mg/L. For continuous infusion, target concentrations between 15 mg/L and 25 mg/L (free concentrations of 4–5× MIC) have been suggested [8,24,25]. The daily maintenance dose (dMD) can be calculated as $dMD = 1440 \text{ min} \times C_{\text{mean}} \times (0.63 \times CL_{\text{Crea}} + 2.8 \text{ mL/min})$, or $dMD = AUC_{24\text{h}} \times (0.63 \times CL_{\text{Crea}} + 2.8 \text{ mL/min})$. Owing to the linear pharmacokinetics of VAN [26], $AUC_{24\text{h}}$ is independent of the dosing regimen (i.e. it is the same whether the daily dose is given as one, two, four or an infinite number of single doses). Therefore, according to classic pharmacokinetic theory the formula should also be applicable to intermittent infusion. Using the Hoek formula, the expression $(0.63 \times CL_{\text{Crea}} + 2.8 \text{ mL/min})$ needs to be replaced by $(0.67 \times GFR_{\text{Hoek}} + 3.2 \text{ mL/min})$. We advise against the use of the Cockcroft–Gault formula for calculating dosing requirements.

Finally, some limitations of this study must be mentioned. This study was performed on a surgical ICU in a university hospital. The majority of patients underwent neurosurgery or general surgery. The results should be extrapolated with caution to other populations.

Calculation of CL_{Van} in this study requires the presence of steady state. Long half-lives make it difficult to attain the real equilibrium, and even impossible if clinical conditions change as is likely in ICU patients. As the individual concentration–time courses were fairly constant and the number of patients with rising or falling concentrations was well balanced, we consider this error small and not systematic.

The dosing recommendations are derived from descriptive data only. Their predictive performance should be validated in prospective studies with heterogeneous populations.

To summarise, we demonstrated in ICU patients that CL_{Van} is closely correlated with measured CL_{Crea} , which is therefore a good basis for estimating dosing requirements. Serum cystatin C may be a useful and practical alternative. Use of the Cockcroft–Gault formula bears large uncertainties in this context.

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Competing interests

None declared.

Ethical approval

Ethical approval was received from the Institutional Ethics Committee of the Charité University Hospital, Campus Benjamin Franklin (reference no. EA4/113/07).

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Fig. 1. Relationship between clearance of vancomycin (CL_{Van}) and (A) measured creatinine clearance (CL_{Crea}), (B) creatinine clearance estimated using the Cockcroft–Gault formula (CL_{CG}) and (C) glomerular filtration rate estimated by the Hoek formula (GFR_{Hoek}). The respective regression equations are shown in Table 2.

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Table 1

Characteristics of the 25 patients (14 male, 11 female) in the study

	Median	Range
Age (years)	59	31–82
Total body weight (kg)	80	45–120
Body height (cm)	173.5	160–187
BMI (kg/m ²)	25.3	16.5–41.5
APACHE II score		
At admission	22	8–36
On study day	19	5–29
SOFA score on study day	8	1–19
CL _{Crea} (mL/min)	106	25–195
Daily dose on the study day (mg)	1500	432–3168
	<i>n</i>	% of total
Focus of infection		
Device-associated meningitis	10	40
Peritonitis or abdominal infection	8	32
Pneumonia	4	16
Osteomyelitis	2	8
Mediastinitis	1	4
Concomitant therapy on study day		
Meropenem	15	60
Ceftazidime	9	36
Rifampicin	9	36
Ciprofloxacin	7	28
Metronidazole	6	24
Fluconazole	4	16
Other antimicrobial agents	15	60
Noradrenaline	17	68
Furosemide	10	40
Mechanical ventilation	22	88

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment; CL_{Crea} , measured creatinine clearance.

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Table 2

Regression equations of the dependence of vancomycin clearance (CL_{Van}) on measured creatinine clearance (CL_{Crea}), creatinine clearance estimated using the Cockcroft–Gault formula (CL_{CG}) and glomerular filtration rate estimated using the Hoek formula (GFR_{Hoek}). Listed are point estimates (95% confidence interval) of (a) slope and (b) y-intercept

	a	b (mL/min)	Coefficient of determination (r^2)	P-value
$CL_{Van} = a \times CL_{Crea} + b$	0.63 (0.53–0.73)	2.8 (–8.0 to 13.6)	0.88	<0.001
$CL_{Van} = a \times CL_{CG} + b$	0.25 (0.11–0.39)	31.3 (9.9–52.7)	0.37	0.001
$CL_{Van} = a \times GFR_{Hoek} + b$	0.67 (0.48–0.85)	3.2 (–15.5 to 21.9)	0.70	<0.001