Patrones de administración de vancomicina en pacientes críticamente enfermos

Vancomycin administration patterns in critically ill patients

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Abstract

Vancomycin is an antimicrobial used in intensive care units for the treatment of Gram-positive cocci infections. The main PK/PD parameter, predictor of vancomycin activity, is the AUC/MIC greater than 400; this is reached with plasma drug concentrations of 15 to 20 mg/l in the context of a patient with normal renal function. In critically ill patients, there are changes in the pharmacokinetic patterns that lead to sub-therapeutic doses of the antibiotic and a requirement for monitoring the vancomycin levels. There was reviewed literature on this field to determine the best vancomycin administration regimen in critically ill patients, and to establish the basic prescription parameters in this population. It was found that continuous infusion of vancomycin was associated with better results since it reached the necessary plasma concentration levels earlier. The loading dose was in the range of 15 to 30 mg/kg and the maintenance dose averaged between 30 to 40 mg/kg per day.

The target plasma concentration of vancomycin used in most of the studies ranged between 15 and 20 mg/l. In conclusion, the continuous administration of vancomycin shows better results compared to intermittent administration. High doses in loading and maintenance are the most recommended since these do not increase the risk of nephrotoxicity. Finally, PK/PD strategies are useful for adjusting the dose of critically ill patients.

Key words: Vancomycin, vancomycin dose, critically ill.

Introduction

Vancomycin is a tricyclic antibiotic produced from Streptococcus orientalis. It has a half-life of 6 to 12 hours, a volume of distribution of 0.4 to 1 L/K, a protein binding of 50 to 55% (1). The distribution to tissues is variable and affected by inflammation and disease states (1). Vancomycin is a compound with a molecular weight of 1450 Dalton. It has no appreciable absorption orally and is eliminated primarily by renal tract with 89 to 90% recovery without changes in urine within 2 hours after administration of a single dose (2).

For several decades, vancomycin has been used for the treatment of infections by Methillin-resistant Staphylococcus aureus, however, the use of this drug is complex due to its behavior based on the patient's own conditions such as age, weight, comorbidities, and especially renal function (3), which cause their pharmacokinetic characteristics to vary the response widely from one patient to another. Vancomycin belongs to the group of glycopeptides, which inhibit the late phase of peptidoglycan synthesis by inhibiting transglycosylation reactions; the primary target of vancomycin is the primary D- ending (4).

The main PK/PD parameter, predictor of vancomycin activity, is the AUC/MIC greater than 400 (5); this is achieved with plasma concentrations of the drug of 15 to 20 mg/l in the setting of a patient with normal renal function and with a MIC less than 1 (5). Monitoring of plasma concentrations should be obtained before the next steady-state dose, that is, before the fourth dose. Monitoring of the peak dose of vancomycin is not recommended (5). Measurement of the plasma concentration of Vancomycin is performed on patients who will receive prolonged treatments for more than 3 days, patients at high risk of nephrotoxicity, patients with unstable pathological conditions and patients receiving high doses of the drug (5).

Patients with critical pathologies experience body changes represented in variations in the water conditions, alterations in the drugs movement and changes in the elimination and metabolism of drugs, which would lead to inadequate antimicrobial concentrations with its respective impact on the clinical response. Similarly, the inappropriate use of antibiotics contributes greatly to bacterial resistance, leading to complications, adverse events, reconsultations and high costs of care. All interventions to improve the quality of prescribing have a positive impact on patient management and the sustainability of health systems (3).

This bibliometric research seeks to know which is the best regimen of administration of vancomycin in critically ill patients, with the aim of determining the basic parameters of the prescription of the same in this population

Materials and Methods.

We searched the literature with the aim of answering the following question: What is the optimal administration regimen of Vancomycin, for critically ill patients? The terms used in the search, both in the English and Spanish languages were Vancomycin dosage, critically ill. The literature search was limited from 2011 to 2021 and used the following search engines: ovid, scopus, pubmed, scielo and Oxford academic. Topic review articles, case reports, meta-analyses, clinical practice guidelines, articles in pediatric and pregnant populations and systematic reviews were excluded from the search. For the evaluation of the articles that were selected, the Strobe declaration was used because all the studies were observational. All the studies were stored in a table containing the type of study, the methodology used and the results of the study.

Results

After searching the various databases, 1561 articles were identified. When applying the exclusion criteria, 55 articles were selected, of which 3 articles were excluded because they were duplicated and 33 articles because they did not contain information that answered the question proposed. The selected articles were critically evaluated with the recommendations of the Strobe declaration, obtaining a total of 19 articles selected for review.

The selected studies were descriptive, observational, retrospective, and prospective. Three important aspects were identified to evaluate in the way vancomycin was dosed in critically ill patients; the first, consisting of the form of administration, either in continuous infusion or in extended or intermittent infusion; the second related to the loading and maintenance dose given to this type of patient and the third the value of optimal plasma concentrations for critically ill patients.

For the form of administration, 4 studies that compared intermittent infusion against continuous infusion were identified. In all four studies, continuous infusion was higher to achieve earlier and more sustained steady-state plasma vancomycin concentrations, with a lower rate of adverse reactions compared to intermittent infusion (Table 1). In three of the four studies, the sample size for the continuous infusion was higher, however, in the study

by Wysocki et al (6) conducted in France, the distribution of patients was more uniform; in this study, 119 patients were enrolled, of which 58 went to the intermittent infusion and 61 to the continuous infusion; the target vancomycin serum concentration was 10 – 15 mg/l for extended infusion and 20 – 25 mg/l for continuous infusion. The duration of the extended infusion was on average 1 hour; the loading dose was 15 mg/K and the maintenance dose was 30 mg/K per day for continuous infusion and 15 mg/k every 12 hours for intermittent infusion. The conclusion of this study is that continuous infusion was associated with better results in reaching the planned vancomycin concentration levels earlier.

Table 1. Comparative articles between continuous and intermittent infusion.

Continuous and intermittent infusion			
Author	**Country**	**Sample**	**Conclusion**
Wysocki et al. (6)	France	Intermittent: 58 pts. Continuous: 61 pts.	Continuous infusion was more effective in reaching vancomycin concentrations
Blot et al. (7)	Australia (Multicentric)	Intermittent: 18 pts. Continuous: 24 pts.	Continuous infusion was superior compared to intermittent infusion.
Tafelski et al. (8)	Germany	Intermittent: 49 pts. Continuous: 76 pts.	Continuous infusion was more effective with lower rate of ADR*
Van Maarseveen et al. (9)	Países bajos	Intermittent: 27 pts. Continuous: 44 pts.	Continuous infusion was superior to intermittent infusion.

*ADR: Adverse drug reactions; pts. Patients

For the loading and maintenance dose, 7 articles in continuous infusion were identified (Table 2). The sample size of the articles is variable, ranging from 22 to 348 patients; the loading dose used in these studies ranges from 15 mg/k to 35 mg/k, being an effective dose to reach plasma concentrations of vancomycin in most studies, except in Commandeur et al (10), where the loading dose administered to 66 patients was 15 mg/k and the planned objective was not achieved.

In three of the seven studies, a high loading dose (greater than 30mg/K) was used, showing high effectiveness in reaching steady status early. In Spadaro's study (11) the load was much lower, compared to the other investigations, because they sought the optimal dose in critical patients with compromised renal function, managing to demonstrate that the nomogram of dose adjusted to creatinine clearance was adequate to reach plasma con-

centrations. The maintenance dose ranged from 20 to 40 mg/k in the seven studies, being stratified based on renal function as shown by Spadaro (11); all research except the one of Commandeur et al (10) demonstrated effectiveness at the doses used. The study by Jason and collaborators (12) represented the largest sample found with 206 septic patients, where they administered high doses of both loading and maintenance in continuous infusion; finding that steady-state vancomycin concentrations of 20 mg/l were reached early on.

Table 2. Comparative articles of loading and maintenance dose in patients receiving continuous vancomycin infusion.

Continuous vancomycin infusion				
Author	**Sample**	***LD (mg/k)**	**DM (mg/K/d)**	**Conclusions**
Jason A et al. (12)	206 pts.	35	35	High doses reach early VPC.
Carricajo et al. (13)	22 pts.	30	30	The dose was effective to reach the VPC.
Commandeur et al. (10)	66 pts.	15	40 a 60	The dose was not effective in the 50% to reach the VPC.
Baptista JP (14)	104 pts.	15	30	The VPC was reached at the studied doses.
Spadaro S (11)	348 pts.	10 - 15	DCr: >50 ml/min: 28; 20-50 ml/min: 20; 10 a 20 ml/min: 15; <10 ml/min: 5-7.	VPC was achieved independent from renal function.
Lin et al. (15)	26	25	30	Effective in obese pts to achieve VPC.
Cristallini et al. (16)	107	35	20 – 40	Effective dose to reach VPC.

*LD: Loading dose; MD: Maintenance dose; Ccr: Creatinine clearance; pts. Patients; VPC: Vancomycin plasma concentrations.

Eight studies used intermittent infusion as a form of administration of vancomycin; the sample size of the studies ranged from 31 to 280 patients, except for the study by Setiawan et al. (17) which analyzes a pre-existing database of 1000 samples of critically ill patients receiving vancomycin (Table 3). The loading dose used was in the range of 15 to 30 mg/k, slightly lower than that reported by continuous infusion studies and the maintenance dose was given on average between 15 to 20 mg/K every 12 hours. In seven of

«Eight studies used intermittent infusion as a form of administration of vancomycin; the sample size of the studies ranged from 31 to 280 patients.»

the eight studies, steady-state concentrations were achieved at the doses administered, except in the study by Villanueva et al (18) where a sample of 197 patients at a loading dose of 25 mg/k and a maintenance dose of 15 to 20 mg/k every 12 hours, did not achieve the planned objectives. The average time of infusion of the drug was between 60 to 120 minutes.

Table 3. Comparative articles of loading and maintenance dose in patients receiving intermittent vancomycin infusion.

Intermittent vancomycin infusion					
Author	Sample	Charge (mg/k)	Infusion time (Minutes)	Maintenance	Conclusions
Setiawan et al.(17)	10000 muestras	---	120	20 mg/k/ each 12 hours	High doses to reach VPC.
He J. (19)	280 pts.	25	120	* High Ccr: 46 mg/K; Normal Ccr: 35 mg/k	High doses at increased Ccr are adequate
Dinh. (20)	55 pts.	25	90	Low Ccr: 15-20 mg/k/d; Normal Ccr: 50 mg/k/d	High loading dose, to achieve VPC.
Rosini J et al. (21)	99 pts.	30	60	15 mg/k/d each 12 hours	High loading dose to reach earlier steady-state VPC.
Kovacevic et al. (22)	73 pts.	25-30	60	15 mg/k/d each 12 hours	PK/PD models are useful to reach VPC.
Álvarez CA et al. (23)	137 pts.	15 -20	90	30 mg/k/d	Adequate doses to reach SVC with lower incidence of ADR
Villanueva RD et al. (18)	197 pts.	25	90	15 – 20 mg/k each 12 hours	VPC was not reached
Truong J et al. (24)	31 pts.	25-30	----	-----	High loading doses to reach VPC

* Ccr: Creatinine clearance; pts. Patients; VPC: Vancomycin plasma concentrations; ADR: Adverse drug reactions.

The plasma concentration of vancomycin used in all studies ranges from 15 to 20 mg/l (Table 4), except in the research of Carricajo et al. (13), where a high target of 30 mg/l was used; This research recruited 22 patients whose creatinine clearance was above 50 ml/minute, concluding that the doses used reach these concentrations at steady state in the 24 hours of administration of the drug. Similarly, for the study by Wysocki et al. (6) the target concentrations used were variable, for extended infusion it was 10 to 15 mg/l, while for continuous infusion it was higher (20 to 25 mg/l); these patients were admitted to intensive care with diagnoses of pneumonia in 45% and bacteremia in 35%, the rest with other infectious conditions; however, both forms of administration were comparable in clinical efficacy and safety.

Table 4: Plasma concentrations of the studies.

Author	concentration (mg/l)	Author	concentration
Jason A et al. (12)	20	Spadaro S (11)	15 – 20
Setiawan et al.(17)	15- 20	Blot et al. (7)	>15
He Juan et al. (19)	> 10 y > 15 CG	Rosini J et al. (21)	>15
Wysocki et al. (6)	IE:10–15; IC:20–25	Lin et al. (15)	15 - 25
Carricajo et al. (13)	30 mg/l	Cristallini et al. (16)	20-30
Commandeura (10)	>25	Tafelski et al. (8)	10-20; 15-20 CG
Dinh et al. (20)	20 – 30	Kovacevic T (22)	15-20
Baptista JP (14)	20 – 30	Álvarez et al. (23)	15-20
Villanueva et al. (18)	15- 20	Truong J et al. (24)	15-20
Van Maarseveen (9)	15-20		

In the study by Tafelski et al (8), broader targets of 10 to 20 mg/l were used for moderate infections, supported under the risk of nephrotoxicity; in severe cases, the target was extended from 15 to 20 mg/l. Both therapeutic objectives were achieved with the doses administered and the route of administration used.

Discussion

Critically ill patients have pharmacokinetic changes that impact the microbicidal effect of antimicrobial therapy. The best parameter for measuring vancomycin is the AUC/MIC greater than 400, being the plasma concentrations of 15 to 20 mg/l the most related to this value and representing the drug concentration in the steady state, with the lowest risk of toxicity. Lower concentrations are accepted in patients with renal failure, however, they should not be below 10 mg/l. There is no clear agreement on the dose to be use; in some cases, adjustment normograms are used depending on the patient's own conditions such as renal function. The recommended dose according to vancomycin monitoring guidelines (2,25,26) is 15 to 20 mg/k every 8 to 12 hours, adjusted according to the result of plasma levels; similarly for critically ill patients, a loading dose of 25 to 30 mg/k (2,25,26) is recommended.

Patients with high-severity pathologies have structural changes in the water compartments, in protein concentrations and in the purification capacity of both renal and hepatic, leading to changes in the concentrations of the drug with an impact on the clinical benefit and the presentation of adverse reactions. Our search found very similar data to what was previously recommended; plasma concentrations in most studies range from 15 to 20 mg/l; some investigations use higher plasma concentration targets

(6,13,10,20,14,15,16), due to pharmacokinetic changes in critical patients and susceptibility to germs in intensive care units.

The loading dose is necessary to reach steady state earlier; on average before the fifth half-life. Loading doses greater than 20 mg/k were found in our search; this is argued in the changes presented by critical patients in renal function. Creatinine clearance is elevated, leading to low plasma levels of drugs that are eliminated by this route; vancomycin, under conditions of hyperfiltration leads to decreased plasma levels.

Studies such as that of Kuti et al. (27) and Pate et al. (28), support the use of vancomycin in intermittent infusion at doses of 4 grams per day for methicillin resistant Staphylococcus aureus (MRSA) with elevated MIC; this data contrasts with our results, where the use in continuous infusion is recommended. Vancomycin has a mixed pharmacokinetic/pharmacodynamic behavior (PK/PD), that is, it is a time-dependent concentration, which makes it have similar characteristics to the beta-lactams, without belonging to this group, having better optimization of its bactericidal action by being in high plasma concentrations above the MIC, which explains the results of the various investigations found in our search.

The maintenance dose found was on average of 30 mg/k a day divided into two or three administrations; which is related to what is recommended in the management guidelines (2,25,26); however, high doses such as those used in the study by Dinh et al. (20) are supported by the changes in hyperfiltration and increased cardiac output presented by these patients. The study by Fernández de Gatta et all. (29) recruited patients with hematological neoplasms with infection by different species of Staphylococcus and different stages of renal function; it concluded that according to the Monte Carlo simulation, high doses of vancomycin of up to 4 grams per day are required, with creatinine clearances greater than 120 ml/minute. High doses of glycopeptide should be considered in cases of infections by Staphylococcus aureus with MIC greater than 1, which correlates in the study of Canut et all. (30), where they took patients from Spain, Belgium and the United Kingdom, with MRSA sepsis, finding that 25% of these infections had a MIC of 2, and the dose of vancomycin required for treatment was 4 grams per day, which was administered 1 gram every 6 hours.

Increased renal clearance in critically ill patients was described in the study by He Juany et all. (19), where they used doses of 46 mg/k day to achieve low therapeutic levels, of 10 mg/l and 15 mg/l for severe cases.

«Studies such as that of Kuti et al. (27) and Pate et al. (28), support the use of vancomycin in intermittent infusion at doses of 4 grams per day for methicillin resistant.»

High doses of vancomycin with low plasma concentration values were used in this study; this is explained by the increase in the elimination of the drug given by the phenomenon of hyperfiltration. This data is similar with the study of Udy et all. (31) where they show that 65% of patients admitted to the intensive care unit have elevated creatinine clearance with subsequent low vancomycin concentrations (p <0.01) when daily doses less than 30 mg/k are used. For the study of Ocampo Martínez et all. (32), a high proportion of insufficient vancomycin concentrations was reported, due to a rapid elimination of the same and a decrease in the half-life of the drug, secondary to hyperfiltration. In addition, low concentrations of vancomycin lead to a decrease in the area under the curve as a pharmacokinetic parameter of absorption and a poor pharmacodynamic response of the drug; the study recommends high doses of vancomycin to counteract this phenomenon. For cases of renal failure with decreased creatinine clearance, the study by Spadaro et all. (11) shows a dose adjustment in accordance with the creatinine clearance values, with no increase in adverse reactions. The target plasma concentration used in this research was 15 to 20 mg/l, however, in patients with dropped glomerular filtration rate, the goal can be extended up to 10 mg/l2 (2).

The risk of nephrotoxicity is associated with high levels of vancomycin, however, in our review no increase in adverse drug reactions was found, even when using high doses of vancomycin, as shown by the study by Jason et all. (12). Intermittent regimens of vancomycin administration show linear increase in the risk of renal toxicity compared to the continuous dose, as shown by Patel's study (28), where vancomycin doses of 1, 2, 3 and 4 grams per day were administered at intervals of 12 hours, with renal function compromise in 10, 16, 25 and 34% respectively.

Dose adjustment strategies according to the PK/PD principles and the Monte Carlo simulation are effective mechanisms to achieve the planned concentrations of vancomycin in critically ill patients. Kovacevic et all. (22) recruited patients who received vancomycin in 1 hour extended infusion, applying PK/PD models, to achieve plasma concentrations of 15 to 20 mg/l;

it concluded that this strategy was effective, and the calculated average dose was 1 gram every 12 hours. PK/PD strategies, at the moment, are widely used to address patients receiving any type of antimicrobial within the context of safe drug use.

Conclusions

The continuous infusion form of administration shows better results compared to intermittent administration; high doses in both load and maintenance were recommended, without increasing the risk of nephrotoxicity. PK/PD strategies are useful for dose adjustment of critically ill patients, with optimal results.

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