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Therapeutic monitoring of vancomycin

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ABSTRACT. The present study aimed to characterize admitted patients in a public hospital in the Northwestern region of Paraná State, which were subject to therapeutic monitoring of vancomycin during 2007 and 2008. The data were obtained by a retrospective study of patients' medical records, from where we separated the laboratory results, medical prescriptions, gender, age, and diagnosis of patients submitted to therapeutic monitoring. Of the total of 38 patients, only eight (21.1%) presented serum concentrations within recommended range, varying from 1.3 to 47.9 mg L^{-1}. Concentrations above the reference value were observed in 22 patients (57.9%), and below the reference, in other eight patients (21.1%). The recommended serum concentrations at peak were obtained in only four patients (11.4%), higher than the recommended value in seven patients (20.0%), and lower, in 24 patients (68.6%). Only one patient (2.6%) presented serum concentration within the reference values at both high and low dosages. Therefore, the results evidenced the importance of therapeutic monitoring of vancomycin, individualizing the dose for each patient, and reducing toxic or subtherapeutic effects of this antimicrobial substance.

Keywords: drug monitoring, staphylococcal infections, vancomycin.

Monitorização terapêutica da vancomicina

RESUMO. O objetivo deste trabalho foi realizar a caracterização dos pacientes internados em um hospital público da região Noroeste do Estado do Paraná que foram submetidos à monitorização terapêutica da vancomicina no período de 2007 a 2008. Os dados foram obtidos por meio de um estudo retrospectivo dos prontuários dos pacientes. Foram separados para este estudo os resultados laboratoriais, prescrições médicas, gênero, idade e diagnóstico dos pacientes que foram submetidos à monitorização terapêutica de vancomicina. Do total de 38 pacientes, em apenas oito (21,1%) as concentrações séricas no vale se encontravam na faixa recomendada variando de 1,3 a 47,9 mg L^{-1}. Foram observadas concentrações acima do valor de referência em 22 pacientes (57,9%) e concentrações abaixo do valor de referência em outros oito pacientes (21,1%). As concentrações séricas recomendadas no pico foram obtidas em apenas quatro pacientes (11,4%), acima do valor de referência em sete pacientes (20,0%) e abaixo em 24 pacientes (68,6%). Apenas um paciente (2,6%) apresentou o nível sérico de vancomicina dentro do valor de referência em ambas as dosagens de pico e vale. Diante desses dados, confirmamos a necessidade da realização da monitorização terapêutica da vancomicina, individualizando a dose minimizando os efeitos tóxicos ou subterapêuticos do antimicrobiano.

Palavras-chave: monitoramento de medicamentos, infecções estafilocócicas, vancomicina.

Introduction

Vancomycin is soluble and complex tricyclic glycopeptide antibiotic, obtained from *Streptococcus orientalis*, with bacteriostatic action against gram-positive cocci and bacilli (HAMMETT-STABLER; JOHNS, 1998). Its use is indicated for the treatment of infections caused by staphylococci or other beta-lactam resistant gram-positive bacilli, in patients allergic to penicillin or who have not responded to treatment with other drugs, including penicillins or cephalosporins. It is predominantly used for the treatment of methicilin-resistant staphylococcal infections, such as brain abscess, staphylococcal meningitis, peritonitis associated with continuous ambulatory peritoneal dialysis, and sepsis. It is used isolated or combined with aminoglycosides in the treatment and prophylaxis of endocarditis, as prophylaxis in patients subjected to surgical procedures and in the treatment and management of immunocompromised patients (LOPES, 2007; MARTINDALE, 2009).

The vancomycin has as mechanism of action the inhibition of cell wall synthesis of sensitive bacteria, and has rapid bactericidal action on the organism in

division. The resistance of enterococci to vancomycin is by the presence of an enzyme that changes the precursor unit of the cell wall so that it no longer binds to vancomycin (RYBAK, 2006). Several strains of *Staphylococcus haemolyticus* and *Lactobacillus* sp. with high degree of resistance to vancomycin were isolated (CHAMBERS, 2006). Essentially, all species of gram-negative bacilli and of mycobacteria are resistant to vancomycin (CUNHA; RISTUCCIA, 1983).

The determinants of resistance to vancomycin for *Enterococcus faecium* and *E. faecalis* are located in a conjugated plasmid and, therefore can be transferred to other enterococci and for other gram-positive microorganisms (CHAMBERS, 2006).

The vancomycin has been used, including pediatric patients, since 1950, but it is in disuse from 1960 due to the adverse effects caused by impurities in the formulation, such as the red man syndrome, ototoxicity and nephrotoxicity (DE HOOG et al., 2004). The interest in vancomycin resurged by the emergence of coagulase-negative-staphylococci as a clinically significant pathogen in neonatal sepsis and the appearance of *Staphylococcus aureus* and *Staphylococcus epidermidis* resistant to methicillin, although there are recommendations for restricted use by the emergence of vancomycin-resistant enterococci (HAMMETT-STABLER; JOHNS, 1998; STEVENS, 2006).

The therapeutic drug monitoring is based on the fact that the therapeutic response is correlated with and depends on the drug concentration in the bloodstream of the user, instead of administered dosage. The use of regular dosages at periodic intervals does not mean constant levels in all patients, due to individual differences in absorption, metabolism, excretion and bioavailability for the administered drug, influencing the final therapeutic effect (LIMA, 1992).

Furthermore, in some cases the therapeutic range, which indicates concentration values for which the substance is pharmacologically useful, is close to the toxic dose, in which there are complications in the context of the patient's health that can lead to intoxication and later to death. Therefore it is necessary the therapeutic drug monitoring in the patient's bloodstream. This monitoring brings the advantage the possibility of adjustments in the dosages of the drug, preventing intoxication, when the drug concentration is above the therapeutic range; and ensuring the pharmacological effects of the substance, avoiding that the concentration remains below it. Thus, the therapeutic drug monitoring promotes safety to drug therapy (PEREZ, 2002).

The criteria for vancomycin monitoring are not as evident as for the other drugs, but the practice to routinely monitor serum concentrations, at peak and trough concentration, is applied as a way to monitor the effectiveness and the emergence of toxicity (BEGG et al., 2001).

The routine practice of monitoring the serum concentration of vancomycin has been subject of intense debate for several years. The controversy resulted in conflicting evidences about the use of vancomycin serum concentrations to predict and prevent drug-induced toxicity and a measure of efficacy in treating infections (RYBAK et al., 2009). The therapeutic range for this antimicrobial agent is also controversial, but usually it is recommended that concentrations between 30 and 40 mg L^{-1} at peak, and concentrations between 5 and 10 mg L^{-1} at trough that refer to antimicrobial concentration needed to achieve the minimum inhibitory concentration (MIC) of the pathogen during the dosing interval (DE HOOG et al., 2004; LUNDSTROM; SOBEL, 2004).

The resistance to vancomycin is a growing problem, particularly in hospitals. Once the vancomycin is a last generation antibiotic for several gram-positive bacteria, the increasing resistance may lead to the previous unwanted scenario, when bacterial infections were mostly fatal (TOBIN et al., 2002).

Because of the need and importance of using the vancomycin in several disease states, the goal of this study was to perform a characterization of the patients, hospitalized in a public hospital located in Northwestern region of Paraná State, subjected to therapeutic monitoring of vancomycin in the years 2007/2008, as well as of the results of the laboratory analysis of these patients.

Material and methods

Studied population

For this study, we surveyed 38 patients admitted in a public hospital located in Northwestern region of Paraná State, which performed the serum dosage of vancomycin in the period of 2007 and 2008. Considering that some of these patients performed more than one test, it was amounted 144 determinations over these two years.

Data gathering

From the dosages of vancomycin performed by the Toxicology Laboratory of the State University of Maringá, the name of the attended patients in the public hospital were identified, for which the analysis was required. With the names, the studied

variables were obtained through a retrospective study of the medical charts of these patients filed in the Service Records of Patients (SRP), relative to the years of 2007 and 2008. For this study, it was set apart the following variables: laboratory results, medical prescriptions, gender, age, and pathology of the patients subjected to therapeutic monitoring of vancomycin.

Compliance with ethical issues

Recognizing the importance of the requirements contained in the Resolution number 196/96 of the National Council of Health, this study was subjected to (Certificate of Ethical Presentation and Appreciation, number 0003.0.093.000-09) and approved by the Committee on Ethics in Research with Human Subjects, under the Opinion number 011/2009 of the State University of Maringá.

Results and discussion

This study is result of the analysis of medical charts of patients hospitalized in a public hospital located in Northwestern region of Paraná State, subjected to therapeutic monitoring of vancomycin in the period of 2007 and 2008. In this period, 38 patients were identified, 16 in 2007, and 22 in 2008.

According to the data presented in Table 1, it was observed that 12 patients were female (31.6%) and 26 patients were male (68.4%), especially those belonging to the age group above 60 years (31.6%). The youngest patient was a child of 10 years, and the oldest, a man of 87 years, the average of ages was 52 years. As described in literature, the natural decrease in glomerular filtration that occurs in elderly people may lead to the raise in serum concentration of vancomycin, corroborating the importance of therapeutic monitoring for these patients that should have the drug dosage adjusted.

Table 1. Distribution of the patients studied according to gender and age.

Variables	Frequency	Percentage
Gender		
Male	26	68.4
Female	12	31.6
Age		
< 11 years	1	2.6
11 - 20 years	1	2.6
21 - 30 years	3	7.9
31 - 40 years	6	15.8
41 - 50 years	6	15.8
51 - 60 years	9	23.7
> 60 years	12	31.6

Eighteen different diagnoses were observed, among them: pneumonia (12 patients), acute abdomen (3 patients), Guillain-Barré syndrome (3 patients), and others.

In order to evaluate which pathogens were involved, it was analyzed all the results of the microbiological cultures of the patients that used vancomycin in the period studied, and the several diseases treated. Nine of the cultures (23.7%) were negative, 12 (31.6%), positive for other infectious agents, and 17 (44.7%) positive for staphylococci. Among the infections by staphylococci, seven (18.5%) patients had infections by MARSA (methicillin-resistant *S. aureus*) and only one (2.6%) progressed to hospital discharge after treatment of infection (Table 2).

Table 2. Distribution of infectious agents identified in microbiological cultures and the progression of the patients.

Result of the culture	Progression		Total
	Discharge	Death	
Negative	2	7	9
Sub-total	2	7	9 (23.7%)
Positive			
S. haemolitycus	1	0	1
MARSA	1	6	7 (18.5%)
S. aureus	2	2	4
Estafilococo-coagulase negativa	1	3	4
S. epidermidis	0	1	1
Sub-total	5	12	17 (44.7%)
Acinetobacter baumannii	1	5	6
A. baumannii / Escherichia coli	0	1	1
A. baumannii / Enterobacter cloacae	0	1	1
Enterobacter cloacae	0	1	1
Pseudomonas aeruginosa	2	0	2
Haemophylus influenzae	0	1	1
Sub-total	3	9	12 (31.6%)
Total	10 (26.3%)	28 (73.7%)	38

The vancomycin is administered intravenously. A single dose of 1 g in adults produces plasma concentrations of 15 to 30 mg L^{-1} after 1-2h of infusion. The vancomycin has serum elimination half-life of about 6h, and can be found in several body fluids including cerebrospinal fluid when the meninges are inflamed (7 to 30%), bile and fluids pleural, pericardial, synovial, and ascitic. More than 90% of the injected dose are eliminated by the kidneys, and may cause adverse effects if renal function is compromised. Besides that, patients with impaired liver function are candidates to adjustment in the doses, since they eliminate the vancomycin more slowly (CHAMBERS, 2006).

The dosage of vancomycin is determined by several clinical and pharmacokinetics factors of the drug. Among the clinical factors, stand out the site and severity of infection, the infectious agent, the underlying disease and concomitant therapies. Regarding the pharmacokinetics it is recommended to monitor the serum levels after three days of the therapy beginning. The vancomycin gets accumulated in the first three to four days of treatment and after this period, it is observed the

steady-state serum concentration, in which is recommended the first collection to evaluate the beginning of the treatment with vancomycin (HAMMETT-STABLER; JOHNS, 1998).

The 38 patients hospitalized and subjected to therapeutic monitoring of vancomycin performed 144 determinations, an average of 3.7 tests per patient. Among them, 68 were carried out in peak, and 76, in trough concentration. Some patients performed only one test in the trough concentration, whereas other ones performed up to 21 determinations. Given this large variation in the number of tests done for each patient, it was chosen for this study only the evaluation of the first dose.

The therapeutic range most often cited for monitoring of vancomycin in the peak and trough and used in this study were the intervals between 5 and 10 mg L^{-1}, and 30 to 40 mg L^{-1}, respectively (LUNDSTROM; SOBEL, 2004). The Table 3 lists the distribution of the patients according to the laboratory result of the first monitoring according to therapeutic range.

Table 3. Result of the first monitoring of vancomycin.

Therapeutic range	Trough concentration		Peak concentration	
	Frequency	%	Frequency	%
Below	8	21.1	24	68.6
Within	8	21.1	4	11.4
Above	22	57.8	7	20.0
Total	38	100.0	35	100.0

The results of the doses showed that the trough serum concentrations ranged from 1.3 to 47.9 mg L^{-1}. It was observed concentrations within the recommended values for eight patients (21.1%), concentrations above the therapeutic range recommended in 22 patients (57.8%), and concentrations below the therapeutic range recommended in eight patients (21.1%). This variability in vancomycin serum concentrations indicates that the monitoring is necessary to ensure that the dosage is suitable for each patient (THOMSON et al., 2009).

By analyzing the results of the peak serum concentrations, we observed that only four patients (11.4%) presented dose within the therapeutic range, seven patients (20.0%), values above, and 24 patients (68.6%) below the recommended range. Also there was a variation in serum concentration between 14.3 and 55.7 mg L^{-1}, and only one patient (2.6%) reached the suitable serum level in both doses of vancomycin in the peak and trough (Table 3). In agreement with the results found by Weinben (1999), it was registered that the serum concentrations presented great individual variation, despite the rigorous recommendations regarding the dosage and technique of administration.

Recently, Rybak et al. (2009) published a consensus on the therapeutic monitoring of vancomycin in adult patients. These authors recommend the trough serum concentration between 15 and 20 mg L^{-1}. Nevertheless, higher concentrations could be necessary for some infections or under situations where a poor penetration of the antimicrobial agent has been described. It was also suggested that trough serum concentrations of 10 mg L^{-1} of vancomycin should be maintained to prevent the development of resistant strains. If this study had considered such recommendations, we would have 28 cases below 15 mg L^{-1}, including 16 below 10 mg L^{-1}, which could be selecting resistant strains and contributing to a worrying lack of success in the treatment.

The trough serum concentration of vancomycin intends to diagnose inadequate levels or subtherapeutic serum concentrations, and concentrations higher than 30 mg L^{-1} are potentially nephrotoxic (VACHER et al., 2002). It has been suggested an association between the increased concentrations of vancomycin in the trough concentration and nephrotoxicity. Usually, patients receiving high doses of vancomycin or when associated with other nephrotoxic drugs may develop renal failure. However, such lesions are infrequent in patients without any other concomitant risk factors (HAZLEWOOD et al., 2010).

Currently, routine practice of determining maximum serum concentrations has been discarded (RYBAK, 2006). However, this determination has been recommended for those patients with alterations in renal and liver functions, obese patients, elderly, and those receiving therapy with other nephrotoxic agents (ACOG, 2009).

The variations in the vancomycin serum concentration and even the possible emergence of adverse effects have led to changes in the drug prescription. Among the adverse effects considered, we evaluated the impairment in renal function. For this, the results of the measurements of urea and creatinine done by patients before, during and after the use of vancomycin were analyzed. According to the Table 4, among the 38 patients that used vancomycin, 16 (42.1%) patients had significant impairment in renal function, being necessary to correct the prescriptions of 13 patients, resulting in a percentage of 81.3% of prescription's correction. Of the 22 (57.9%) patients without alteration in renal function, it was also necessary to correct the prescriptions of 13 (59.1%) patients. In total, it was

necessary to correct the vancomycin prescribed dose in 26 patients (68.4%).

Table 4. Evaluation of medical prescriptions and alteration in renal function after the serum dosage of vancomycin.

Prescription	Renal function		Total	
	Altered	Without alteration	Frequency	Percentage
Corrected	13	13	26	68.4
Without correction	3	9	12	31.6
Total	16 (42.1%)	22 (57.9%)	38	100.0

Dell'Aquilla et al. (2004) described strains with MIC of 2 mg L^{-1} and despite the low value obtained for the MIC, the plasma concentration achieved from the sixth hour of the administration would not be enough for bactericidal action. Besides that, it should be considered that the vancomycin has time-dependent bactericidal action, i.e., its serum concentration should be above the MIC at about four times, and as it decays below this value, the bactericidal action is lost, which may lead to therapeutic failure.

It is worth emphasizing that this study was performed with patients with severe sepsis, thus obtaining a high percentage (73.7%) of deaths. Despite the minimal chances of survival, perhaps if the therapeutic monitoring of vancomycin had been done more effectively with adjustment of dosages, a greater success in the treatment could have been achieved.

According to Rybak et al. (2009), the therapeutic monitoring should begin just before the fourth dose for all patients with prolonged use of the substance, by pharmacokinetic and pharmacodynamic factors; and there is no ideal dose for vancomycin, so, one should consider a series of clinical factors for each case and patient. In the studied patients, we observed that the first dose was performed in the recommended period (*steady-state*) in 15 patients (39.5%). In the other patients, this criterion was not obeyed, being done the first dose of therapeutic monitoring with more than four days in 13 patients (34.2%) and with less than three days in ten patients (26.3%) as presented in Table 5.

Table 5. Number of days between the start of the treatment and the first dosage of vancomycin.

Days	Number of patients	Percentage
< 3 days	10	26.3
3 to 4 days	15	39.5
> 4 days	13	34.2
Total	38	100.0

For this reason, it is very important to ensure that the population candidate to use the vancomycin keep the plasma levels within therapeutic range established by several bibliographies. Thus the patient should be monitored through measuring the serum concentration of vancomycin, individualizing the dose for each patient and case, facilitating the adjustment of the drug and the lower chance of toxic or subtherapeutic effects of the antimicrobial substance, leading to treatment failure and the emergence of bacterial resistance. In this way, the observations carried out in this study corroborate the unpredictability of serum concentrations obtained from recommended doses, pointing out that norms and criteria for monitoring must be objects of concern when using this drug to obtain a satisfactory therapeutic response (RUANO et al., 2005).

Conclusion

The vancomycin is still a safe antibiotic, of easy use and low cost; however its use requires the fulfillment of norms, criteria and an adequate therapeutic monitoring according to each case. Based on the results obtained, we concluded that the therapeutic monitoring of vancomycin should be performed in patients in order to change the dosage regimen to prevent treatment failure and reduce the risk of developing bacterial resistance.

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