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Clinical pharmacy and serum concentration of Vancomycin: from therapeutic monitoring to change of conduct in inpatient units

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Abstract

Objectives: To compare, by means of plasma concentration, the prescribed dose (loading dose and full dose) of vancomycin in patients undergoing hemodialysis at Hospital Santa Casa de Misericordia in Maringa. **Method:** Retrospective cohort study with patients hospitalized from July/2020 to July/2021 who were on renal replacement therapy and used vancomycin. Data were collected from the electronic medical record considering the serum concentrations and clinical information of the patients, being organized in spreadsheets and the comparison of the medians of the two groups performed by the statistical tests of Mann-Whitney and Kruskal-Wallis. **Result:** A total of 51 patients were included in the study, 13 who received a mean loading dose of 19.01 mg/kg and 38 patients with full dose (1,000mg every 8 - 12h) before adjustment for dialysis, with median aged 55 years and 64.5 years, respectively. The amount of pharmaceutical adjustments performed, considering the serum concentration and the number of vouchers performed, were similar in both groups. The first trough obtained was statistically lower in patients with a loading dose (20 µg/mL) when compared to a full dose (33.2 µg/mL). Furthermore, the full dose group presented about 60% of the results of vouchers, during treatment, above the recommended therapeutic range. It was not possible to assess therapeutic failure and patient survival. **Conclusion:** Patients who received a loading dose reached the therapeutic serum level of vancomycin more quickly and with a lower risk of toxicity, remaining within the target during the entire treatment.

Key words: drug monitoring, vancomycin; renal replacement therapy; hospital pharmacy service.

Farmácia clínica e vancocinemia: da monitorização terapêutica à mudança de conduta nas unidades de internação

Resumo

Objetivo: Comparar, por meio da concentração plasmática, a dose prescrita (dose de ataque e dose plena) de vancomicina em pacientes submetidos a hemodiálise no Hospital Santa Casa de Misericórdia de Maringá. **Método:** Estudo de coorte retrospectiva, com pacientes internados no período de julho/2020 à julho/2021 e que estavam em terapia renal substitutiva e fizeram uso de vancomicina. Os dados foram coletados do prontuário eletrônico considerando as concentrações séricas e informações clínicas dos pacientes, sendo organizados em planilhas e a comparação das medianas dos dois grupos realizadas pelo testes estatísticos de Mann-Whitney e Kruskal-Wallis. **Resultado:** Um total de 51 pacientes foram incluídos no estudo, sendo 13 que receberam dose de ataque média de 19,01 mg/kg e 38 pacientes com dose plena (1.000mg a cada 8 - 12h) antes do ajuste para diálise, com mediana de idade de 55 anos e 64,5 anos, respectivamente. A quantidade de ajustes farmacêuticos realizados, considerando a concentração sérica e o número de vales realizados, foram semelhantes nos dois grupos. Já o primeiro vale obtido foi estatisticamente menor nos pacientes com dose de ataque (20 µg/mL) ao comparar com dose plena (33,2 µg/mL). Ademais, o grupo dose plena apresentou cerca de 60% dos resultados de vales, durante o tratamento, acima da faixa terapêutica recomendada. Não foi possível avaliar falha terapêutica e sobrevida dos pacientes. **Conclusão:** Os pacientes que receberam dose de ataque atingiram o nível sérico terapêutico de vancomicina mais rapidamente e com menor risco de toxicidade, mantendo-se dentro do alvo durante todo o tratamento.

Palavras-chaves: monitorização terapêutica, vancomicina; diálise renal; serviço de farmácia hospitalar.

Introduction

Therapeutic Drug Monitoring (TDM), especially of those medications with low therapeutic indices or significant pharmacokinetic variability, aims at maintaining a drug's serum concentrations within the therapeutic range, in order to optimize the therapeutic effect and minimize possible underdoses or toxicities [1] Patients undergoing Renal Replacement Therapy (RRT) represent one of the challenges found in TDM, as the physiological changes that occur in this population significantly affect the pharmacokinetic properties of the drugs, such as Vancomycin, leading to a wide variation in half-life and consequent inadequate concentrations of the medication.[1]

Vancomycin is one of the most studied medications in the TDM practice, due to its potential nephrotoxic effect and its narrow therapeutic range, and because it suffers significant variations in serum concentration as a response to the patient's hemodynamic changes; thus, there are current recommendations in different populations, such as critically-ill, pediatric, renal failure and obese patients.[2-4] Vancomycin is a glycopeptide used in the treatment of infections caused by Gram-positive bacteria, especially by strains of methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative *Staphylococcus* and *Enterococcus faecium*.[5] It has a hydrophilic nature, is eliminated via glomerular filtration, and has an elimination half-life of approximately six hours in individuals with preserved renal function.[2]

Although Vancomycin is commonly used in hemodialysis patients, there are few published results and studies that provide guidance on the optimal pharmacokinetic-pharmacodynamic (PK/PD) targets in this population.[4] Therefore, the objective of this study was to compare Vancomycin plasma concentration in hemodialysis patients that received a loading dose or a full dose.

Methods

This is a retrospective cohort conducted with patients admitted at the Santa Casa de Misericórdia Hospital of Maringá from July 2020 to July 2021 and who were undergoing RRT, in order to assess the prescribed Vancomycin dosage and its serum concentration. This study was approved by the hospital's Commission of Ethics in Medicine and by the Permanent Committee of Ethics in Research with Human Beings of the State University of Maringá (Opinion No. 4,942,548).

Therefore, the study included adult patients undergoing RRT who started using Vancomycin with a loading dose or a full dose. Patients aged less than 18 years old and on RRT in the peritoneal or continuous dialysis modalities were not included. The Santa Casa de Misericórdia Hospital of Maringá is a high-complexity philanthropic institution and a regional reference in Obstetrics, Neurosurgery and Nephrology, with nearly 311 beds, of which more than 60% are devoted to patients served by the Unified Health System (*Sistema Único de Saúde*, SUS).

Vancomycin Therapeutic Monitoring (VTM) was employed in this hospital in 2018 as a pilot implementation in the Intensive Care Unit (ICU). It was subsequently expanded to the wards and to the pediatric unit the following year. Implementation of this service involved the support of the Board of Directors and of the multidisciplinary team, with the clinical pharmacist being responsible for managing and making suggestions for the entire process of the medication dose adjustment.

After implementing VTM, it was verified that the patients undergoing RRT presented higher Vancomycin serum concentrations than the others, with use of the Vancomycin loading dose (20 mg/kg- 35 mg/kg, maximum of 2,000 mg/dose) followed by a maintenance dose (500 mg- 1,000 mg after dialysis) being proposed instead of the full dose (1,000 mg every 8 h- 12 h) followed by adjustment for dialysis. Thus, the data referring to the prescribed Vancomycin dosage were analyzed, including patients on RRT who were prescribed a loading dose or a full dose and who had their plasma levels monitored during the treatment.

In the study institution, collection for assessment of the Vancomycin plasma concentration (trough level) was conducted preferably before dialysis and nearly 12- 24 hours after the loading dose or after completion of the full dose and before adjustment for RRT. The patients were divided into two groups: loading dose group and full dose group, and data such as gender, age (years old), dosage prescribed, serum concentration (µg/mL) results, number of pharmaceutical adjustments and treatment time (days) were collected from the patients' electronic medical records and organized in spreadsheets. A descriptive analysis of the clinical and anthropometric data was performed in Microsoft Excel.

The results of the medians referring to age, number of adjustments, number of troughs, treatment time and first Vancomycin serum concentration were compared between the loading dose and the full dose groups using the Mann-Whitney and the Kruskal-Wallis tests. For the gender variable, Pearson's Chi-square test was employed. Excel was also used to perform the statistical analyses, with those having p-values < 0.05 being considered as statistically significant.

Results

In all, 196 adult patients used Vancomycin during the study period, although only 72 were on RRT. Of these, 51 met the inclusion criteria and 21 were excluded from the analysis (Figure 1). Of the patients who met inclusion criteria, 13 belonged to the loading dose group, of which 8 were men and 5 were women; and 38 patients belonged to the full dose group: 25 men and 13 women. The clinical data corresponding to the patients of this study are shown in Table 1.

Figure 1. Flowchart corresponding to inclusion of the patients in the study.

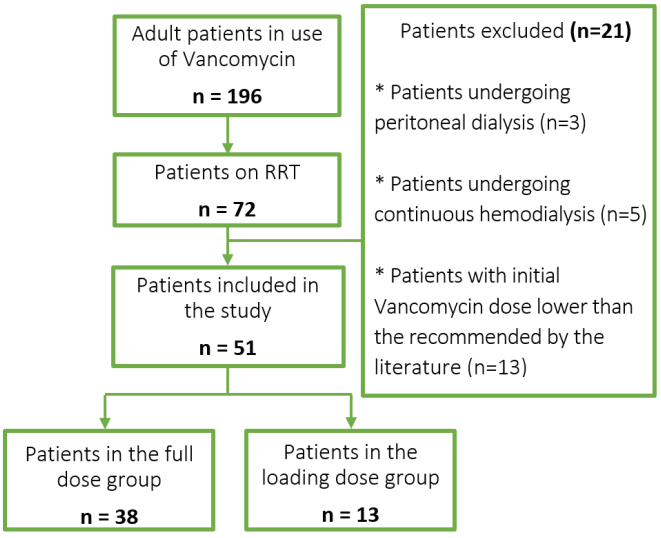


Table 1. Clinical data of the patients on hemodialysis who received the loading or the full Vancomycin dose from July 2020 to July 2021.

Information	Full dose N=38	Loading dose N=13	p-value
Sociodemographic			
Male gender n (%)	25 (65.8)	8 (61.5)	0.9690
Age (years old) Median (P_{25}; P_{75})	64.5 (54.0; 74.2)	55.0 (43.5; 65.0)	0.0929
Pharmacotherapy Median (P_{25}; P_{75})			
Number of adjustments	2.0 (1.0; 3.0)	2.0 (1.0; 3.5)	0.8765
Number of troughs	4.0 (2.5; 6.0)	5.0 (2.5; 6.0)	0.5309
Treatment time (days)	10.0 (5.0; 12.0)	13.0 (5.5; 16.0)	0.1233
Result of 1st trough (µg/mL)	33.2 (27.4; 42.4)	20.1 (14.3; 25.6)	0.0001

The median number of troughs (4 for the full dose and 5 for the loading dose) and of pharmaceutical adjustments considering serum concentration (2 for the full dose and 2 for the loading dose) was similar in both groups. Treatment time was longer with the loading dose, with a median of 13 days versus 10 days in the full dose group. The loading dose used (from 20 mg/kg to 35 mg/kg; maximum of 2,000 mg/dose) was calculated by the prescribing physician, based on the patient's actual weight, with an overall mean of 19.01 mg/kg (Figure 2).

When analyzing the first plasma concentration, it was statistically lower in the patients who received the loading dose ($p<0.05$), as also shown in Table 1. In addition to that, the number of troughs above the therapeutic range (>25 µg/mL) was also lower in the patients receiving the loading dose, with an approximate reduction of 80% when compared to the full dose. For all the patients included in this study, the infections were considered as severe, with a therapeutic Vancomycin target of 15 µg/mL- 25 µg/mL (Figure 3). It was not possible to assess and compare patients' survival after the use of Vancomycin in the different types of prescription, as well as whether there was therapeutic failure with the doses used.

Figure 2. (a) Distribution of the first Vancomycin serum concentration after the loading dose, considering the patients' actual weight. Green: loading dose of approximately 15 mg/kg; orange: 20 mg/kg, and red: 25 mg/kg. (b) Distribution of the first serum concentration before dose adjustment in the patients who received the 1 g 12/12h (blue) or 1g 8/8h (purple) doses.

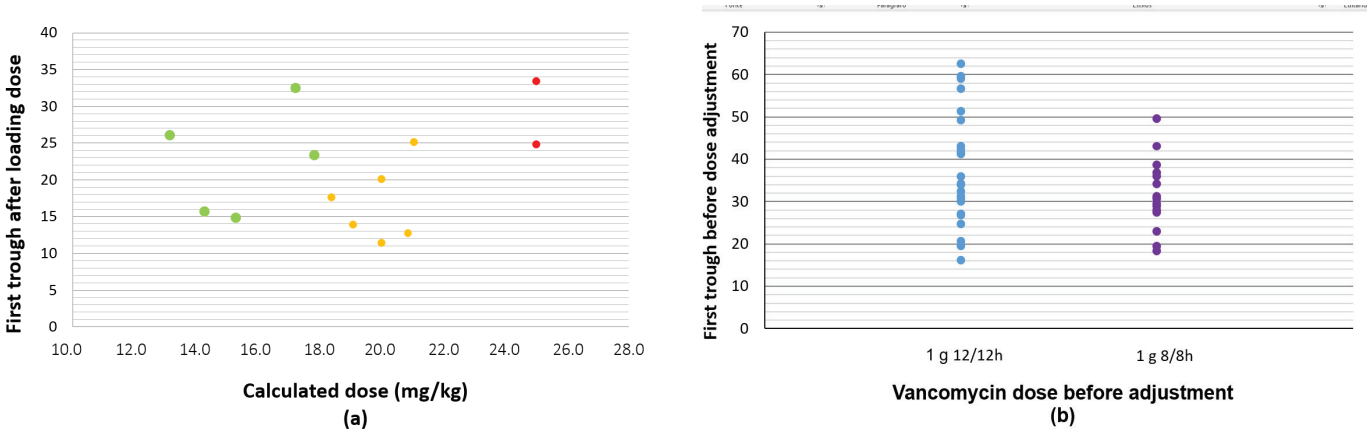
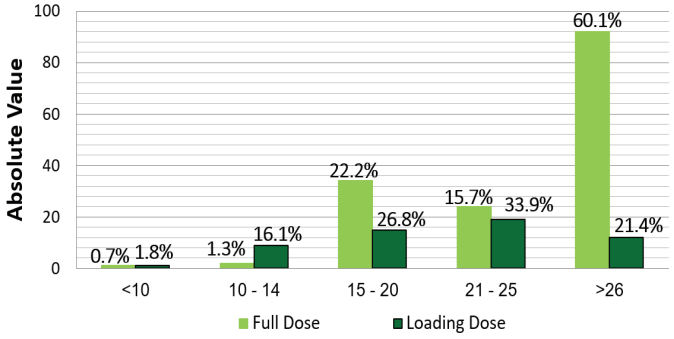


Figure 3. Results of the troughs (µg/mL) during treatment of the patients in use of Vancomycin and on hemodialysis who received the full and loading doses, respectively.



Discussion

With regard to the variabilities in the pharmacokinetics of Vancomycin that affect the drug's plasma concentration and exert an impact on the dosage selected, critically-ill patients with severe sepsis stand out, as well as those on hemodialysis, obese and overweight.[6,7] Therefore, VTM in critically-ill hemodialysis patients is still challenging in the clinical practice. In this study, it was possible to notice that the use of a loading dose contributed to achieving more appropriate therapeutic levels when compared to the use of a full-dose regime.

Although there are few studies elucidating the best approach to reach the Vancomycin serum therapeutic level faster in patients undergoing RRT, the recent guidelines recommend loading doses of 20 mg/kg- 35 mg/kg, based on the patient's actual body weight, for the early achievement of the therapeutic level and consequent steady state.[4] Such course of action also reduces the risk of serum concentrations outside the therapeutic range during the first days of therapy (under- or over-dose), thus being recommended for this population. With regard to the therapeutic serum concentration, a number of studies argue for a range between 15 mg/L and 20 mg/L for moderate to severe infections, which may be extended to a maximum of 25 µg/mL in cases of meningitis and endocarditis.[4,8]

Another point to be considered is the fact that the therapeutic response to Vancomycin depends on its serum concentration and not necessarily on the dose administered, since patients, especially those with impaired renal function, have different responses with regard to absorption, metabolism, excretion and bioavailability of the drug. Therefore, dose adjustment according to serum concentration ensures a better response to the drug, in addition to preventing poisoning and consequent harms, as long as these concentrations are properly obtained and interpreted.[4,5]

The doses used in the patients under study varied from 15 mg/kg to 25 mg/kg, not exceeding 2,000 mg/dose, as defined in the institutional protocol for patients undergoing RRT, a value slightly lower than the one recommended in the literature. Therefore, in some obese patients, a first Vancomycin serum concentration between 10 µg/mL and 15 µg/mL was obtained, thus being below the recommended therapeutic range for severe infections.

The importance of selecting an appropriate dose that reaches a therapeutic PK/PD exposure cannot be underestimated, which may have occurred in the obese patients, as recent studies conducted with this population indicate a reference with a loading dose of up to 3,000 mg. Additionally, pharmacokinetic studies can help physicians select an appropriate empirical dosage regime in order to achieve therapeutic exposures at treatment initiation and potentially improve bacterial elimination while minimizing nephrotoxicity.[3,7]

In relation to the concentration median (20.07 µg/mL) referring to the first monitoring in the group that received the mean loading dose of 19.01 mg/kg, it was close to the one obtained by Brown et al. (17.8 µg/mL), although with a lower mean dose (13.6 mg/kg). These authors also observed that age can be a significant negative predictor of the Vancomycin levels in hemodialysis patients and should thus be considered when selecting the loading dose.[8]

In addition to that, the literature also considers the ratio between the Area Under the Curve (AUC) of the Vancomycin level in the period from 0 to 24 hours and the Minimum Inhibitory Concentration (MIC) (AUC/MIC) for *S. aureus* isolates as an important efficacy indicator.[4,9-11] However, as data showing an ideal AUC target in hemodialysis patients are not available, it is thus recommended that monitoring be based on the pre-dialysis concentrations and to extrapolate these values to estimate an AUC of 400 mg.h/L to 600 mg.h/L.[4]

The study presents some limitations to be considered: the first is related to the size of the population involved, which may have led to estimation errors. It is believed that larger samples, mainly in the loading dose group, would confer more robustness to the findings and conclusion of the diverse evidence. The second limitation deals with the conduction of a single-center and retrospective research study, with data retrieved from medical records, which are often filled out in an incomplete and non-detailed manner. In addition to that, not all trough serum concentrations are collected immediately before hemodialysis. Finally, the third limitation refers to the impossibility of analyzing patients' survival or therapeutic failure, in order to compare the different types of prescription (loading dose and full dose).

Conclusion

The patients who used the loading dose reached the therapeutic target faster than those who received the full dose before adjustment for dialysis, in addition to obtaining fewer concentrations above 25 µg/mL, thus reducing toxicity.

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Collaborators

LGS, ALPS, JKF, AMG and WDF were responsible for conceiving the project. LGS, ALPS and DH were in charge of data analysis and interpretation and were responsible for writing the article. All the authors provided final approval of the submitted and published versions.

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Declaração de conflito de interesses

Os autores declaram inexistência de conflitos de interesses em relação a este artigo.

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