The study of vancomycin use and its adverse reactions associated to patients of a brazilian university hospital

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Abstract

Background: Vancomycin is an antibiotic of growing importance in the treatment of hospital infections, with particular emphasis on its value in the fight against methicillin-resistant Staphylococcus aureus. However its usage profile must be evaluated to assure maximum benefit and minimum risk.

Findings: A cross-sectional retrospective study was carried out among inpatients that received vancomycin in a Brazilian quaternary hospital. The occurrence of adverse reactions reported was evaluated in medical records relating to patients taking vancomycin during a one year period. Males comprised 52% (95% CI: 41.7-60.2%) of the sample population, with a mean age of 50.6 (95% CI: 47.2-54.0) years and mean treatment period of 9.7 (95% CI: 8.0-11.5) Days. It was verified that nephrotoxicity occurred in 18.4% (95% CI: 11.3-27.5) of patients, Red man syndrome occurred in 2% (95% CI 0.2-7.2), while the occurrence of thrombocytopenia was 7.1% (95% CI: 2.9-14.2).

Conclusions: It may be noted that even after 50 years of use, adverse reactions associated with vancomycin continue with high frequency, presenting a public health problem, especially considering its current use in cases of multidrug resistant infections. In this context, we emphasize the importance of intensive pharmacovigilance in hospital as a surveillance tool after drug approval by the sanitary authority.

Findings

Introduction

Vancomycin is a complex glycopeptide antibiotic with an unusual structure and molecular mass of approximately 1500 Da. Vancomycin acts primarily inhibiting the cell-wall biosynthesis. Its action against gram-positive cell walls is related to the prevention of the incorporation of N-acetylmuramic acid and N-acetylglucosamine into the peptidoglycan matrix. Its therapeutic use against infections caused by gram-positive bacteria started in the 1950’s and it is still used currently. During the 1960’s and 70’s its use suffered a large decline, due to the high incidence of adverse reactions and the introduction of semisynthetic penicillins with broadest spectrum of action in the therapeutic arsenal [1]. However, the rapid development of bacterial resistance to semisynthetic penicillin, especially methicillin-resistant Staphylococcus aureus (MRSA), led to the return of the use of vancomycin on a large scale from the 1980’s.

During the following two decades, some studies showed a possible link between the widespread use of vancomycin and a rise in the incidence of adverse reactions, especially nephrotoxicity [1], ototoxicity [2], thrombocytopenia [3,4], epidermal necrosis [5], neutropenia [6], phlebitis [7], and a pathology related to histamine release known as the red man syndrome [8-10], which highlights the need for more effective monitoring of the use of this antibiotic. The reports of Enterococcus faecalis resistant to vancomycin published since the 1990’s, and recently in Brazilian hospitals, further emphasizes the need to rationalize the use of this drug [11]. Others studies have been carried out in order to confirm the safe use of vancomycin, as the recent systematic review that compared vancomycin safety and efficacy with the other available glycopeptide [12]. This study showed the importance of producing more scientific data on vancomycin ADR. Nevertheless, the severity of
these effects is reflected in the constant concern with the monitoring techniques employed and vancomycin's effectiveness when it is used [13]. Therefore, this study evaluates the use of vancomycin and the prevalence of the main adverse reactions in a large university hospital in quaternary care.

Methods

Population studied
The retrospective cross-sectional study population consisted of individuals who had used vancomycin during the period of July 2003 to June 2004, as this data were the most reliable in relation to the storage process and accessible at the time of the study, while attending a university hospital in Brazil. From the total of 350 patients that utilized vancomycin during the study period, a random sample was selected based on the sample size estimation calculated by statacalc tool from epininfo® (version 3.3.2), utilizing 95% of precision. The estimated sample size was 122 patients. Based on that estimate, a random sample of 131 patients was selected as the population for this study. After applying the exclusion criteria, 98 medical records were included for analysis. The study included all individuals older than 18 years, with use of vancomycin confirmed by documentation in their medical records. It excluded mainly those individuals whose records contained insufficient laboratory data to allow assessment of presence or absence of adverse reactions.

Definitions
For measuring and comparing the data regarding the exposure of vancomycin, we utilized as reference the mean daily dose of the drug when used for its main indication, being equal to 2 g of vancomycin [6]. Thus, all the vancomycin exposure data were expressed as grams of vancomycin. Adverse reactions were categorized as: probable (event or laboratory test abnormality, with reasonable time relationship to drug intake, unlikely to be attributed to disease or other drugs, response to withdrawal clinically reasonable, rechallenge not required); possible (event or laboratory test abnormality, with reasonable time relationship to drug intake, could also be explained by disease or other drugs, information on drug withdrawal may be lacking or unclear); conditional (event or laboratory test abnormality, more data for proper assessment needed, or additional data under examination); and uncertain (event or laboratory test abnormality, with a time to drug that makes a relationship improbable, but not impossible, disease or other drugs provide plausible explanations) [14-16].

Ethics
In order to comply with regulations relating to Human Research, requirements regarding the confidentiality and secrecy of the information collected were adhered to. The study was approved by the ethics committee of the Faculty of Medicine of Federal University of Rio de Janeiro, being filed under the number 115/04. The project was approved on 9 September 2004.

Data Collection
A survey was structured through the analysis of the data from the hospital IT system and the reports of the use of antimicrobials archived by the committee of hospital infection control, only standardized forms were used for data collection, and the following variables referenced in the literature were selected as relevant to the occurrence of adverse drug reaction: age [17], sex, serum creatinine [17], use of nephrotoxic drugs [18,19], hypoalbuminemia [19], dose and reason for use. Signs and symptoms of adverse reactions were evaluated using the criteria in Table 1.

The standardized forms contained the following information: Patient ID; date of birth; body weight; height; sex; reason to utilize vancomycin; date of use; daily dose; length of infusion; previous use of vancomycin; laboratory data (total serum proteins; serum albumin; hematocrit; total white blood cells count; neutrophils count; serum creatinine; platelets); other drugs; ADR description; concomitant diseases. The data were collected by one researcher and checked by another to maintain the quality of form filling.

As the cross-sectional design of study has not the ability to establish causality relationship, we screened every detected ADR with two distinct algorithms Karch and Lasagna algorithm and Naranjo & col algorithm, both previously published and already established to classify the probability of occurrence of an ADR, minimizing the risk of bias during the ADR detection process [14,15].

Data analysis
The analysis was performed by comparing the prevalence of adverse reactions between the various strata of this subpopulation [20,21]. The database created to manage the information collected during the hospital records search was set using the epininfo software version 3.3.2 (Centers for Disease Control and Prevention - CDC, USA). The prevalence ratios were calculated by comparing the prevalence of ADR in groups of patients that were/were not exposed to specific risk factors (other drugs, previous vancomycin use, and others). These prevalence ratios were calculated using epininfo® and compared utilizing chi square or the fisher exact test.

Results and Discussion

Prevalence of Adverse Reactions for Vancomycin
The prevalence of adverse reactions to vancomycin observed in medical records is presented in Table 2. From the data collected it was found that 27.6% (95% CI: 19.0 - 37.5%) of the patients treated with vancomycin had
Table 1 Criteria followed for evaluate signs and symptoms of adverse reactions

| Adverse symptoms/reactions | Source                               | Criteria                                                                 |
|-----------------------------|--------------------------------------|--------------------------------------------------------------------------|
| Phlebitis                   | Medical records                      | Indicated by medical personnel                                           |
| Nephrotoxicity              | Medical records/Laboratorial analysis | Serum creatinine concentrations of 0.5 mg/dl or 50% increase over the baseline, whichever is the higher value¹⁴ |
| Neutropenia                 | Medical records/Laboratorial analysis | Neutrophil count below 1,000 cells per cm² of peripheral blood¹           |
| Ototoxicity                 | Medical records/Laboratorial analysis | Indicated by medical personnel after audiometric evaluations and reports of hearing loss after treatment, obtained by attending physicians in the process of anamnesis; |
| Thrombocytopenia            | Medical records/Laboratorial analysis | Platelet count less than 100,000 per microliter of peripheral blood       |
| Red man syndrome            | Medical records                      | Indicated by attending physicians and reviewers, faced with the following standard of diagnosis: flushing, itching, chest pain, muscle spasm or hypotension during infusion of vancomycin |

Table 2 Prevalence of adverse reactions to vancomycin during the study period

| Type of adverse reaction | Number of patients | Percentage | 95% CI (%) |
|-------------------------|--------------------|------------|------------|
| Nephrotoxicity          | 18                 | 18.4       | 11.3 - 27.5|
| Neutropenia             | 2                  | 2          | 0.2 - 7.2  |
| Ototoxicity             | 1                  | 1          | 0.0 - 5.6  |
| Red Man Syndrome        | 2                  | 2          | 0.2 - 7.2  |
| Thrombocytopenia        | 7                  | 7.1        | 2.9 - 14.2 |
which established the prevalence as 0-35% in patients and 70-90% in healthy volunteers. Considering that the occurrence of RMS is directly related to the rate of infusion of vancomycin [20,22,23,27,28], the fact that 60% of patients who used vancomycin had no information in their records regarding the duration of infusion of vancomycin solution shows that there is a dangerous lack of concern or ignorance of this type of ADR and the recommended method of drug administration.

Ototoxicity is an ADR that had a prevalence of 1% (95% CI: 0 - 5.6%) with similar data presented by Farber & col. This study has no recorded occurrence of phlebitis. However the study of Farber & col [2] showed a prevalence of 13% of this ADR, being the second most prevalent. In the study by Hing & col [23] it is presented, in conjunction with pain, as the most prevalent ADR affecting 11% of patients treated with vancomycin. A plausible reason for the low prevalence of ototoxicity is the non-completion of routine audiometric tests in hospitalized patients, which was the real measure of prevalence of this ADR [2].

Sample Characteristics and Vancomycin Exposure

Of the 131 selected patients, 98 were effectively analyzed, as the medical charts of 31 patients had inadequate records, especially regarding to the clinical laboratory data, becoming impossible the verification of signs and symptoms of ADR, and 2 patients were aged less than 18 years, being therefore excluded from the study. Table 3 shows the main characteristics of the population studied and no evidence of clustering in the extremes of age or by sex, which could suggest confounding factors for the prevalence estimate of ADR [16,17].

The data analysis (Table 4) of initial creatinine and serum albumin showed that patients that presented with ADRs did not show any laboratory data at the beginning of treatment that would have identified them as a group at risk of suffering adverse reactions [29].

The main reasons for the use of vancomycin among the studied patients were sepsis 12.2% (95% CI: 6.5 - 20.4%), nosocomial pneumonia 12.2% (95% CI: 6.5 - 20.4%), catheter-associated infection 11.2% (95% CI: 5.7 - 19.2%) and blood culture with Gram positive cocci 11.2% (95% CI: 5.7 - 19.2%). Among patients who had some type of adverse reaction associated with vancomycin, the main reasons for using the drug were septic shock 11.1% (95% CI: 2.4 - 29.2%), nosocomial pneumonia 11.1% (95% CI: 2.4 - 29.2%), endocarditis 7.4% (95% CI: 0.9 - 24.3%) and abdominal sepsis 7.4% (95% CI: 0.9 - 24.3%).

The analysis of the total doses of vancomycin presented in Table 4 shows that there is no significant difference in total dose of vancomycin administered to the group of patients that did present with an ADR compared to those that did not (p >0.05). The analysis of average daily dose of vancomycin also showed no significant difference between the average daily dose given to patients that did and those that did not present with an ADR (p >0.05). Statistical analysis comparing the subgroups of ADR+ and ADR- patients as presented at Table 4 did not present any statistically significant difference (P > 0.05).

Concurrent use of other antimicrobial drugs was also evaluated, since some studies suggest synergism in their ability to cause adverse reactions with vancomycin [18,19,26,29,30]. It was found that cefepime, imipenem/cilastatin and ciprofloxacin were the most commonly used antibiotics in both groups of patients, those that did and did not present with an ADR. Broad-spectrum beta-lactam drugs were the most frequent antimicrobial drugs used in both groups. The prevalence ratio was calculated as an indicator of the synergistic effect of these antibiotics, but none had a statistically significant relation.

The rate of infusion of vancomycin is one of the factors classically associated with the occurrence of adverse reactions [20]. It is recommended that the duration of the solution infusion is not less than 60 min. Thus, the duration of vancomycin solution infusion was included in the analysis of the factors possibly associated with ADRs, and this was categorized as greater than 60 min, less than 60 min or without any record. However it was not possible to ascertain any statistically significant relationship between duration of infusion and the occurrence of ADR. Another worrying fact was the absence of records of the infusion rate of vancomycin solution in 62.24% of the prescriptions of the total population, a fact that suggests that little importance is assigned to the scientific evidence of a higher incidence of cutaneous and systemic adverse reactions in patients with infusion of vancomycin over periods of less than 60 min [8,20,22].

This study is retrospective and only the adverse effects reported in medical records could be evaluated. The absence of data in the medical records could reflect a practice of not reporting some types of ADR, considered

| Characteristics        | Median | Mean | Mean 95% CI (%) |
|------------------------|--------|------|-----------------|
| Age (years)            | 51.5   | 50.6 | 47.2 - 54.0     |
| Treatment time (days)  | 7.0    | 9.7  | 8.0 - 11.5      |
| Total Vancomycin dose (g) | 24    | 18.3 | 12.4 - 23.8     |
| Vancomycin Daily dose (g/day) | 1.9   | 1.9  | 1.6 - 2.4       |
| Initial creatinine (mg/dl) | 1.0   | 2.0  | 1.5 - 2.5       |
| Albumin (g/dl)         | 1.8    | 1.9  | 1.6 - 2.1       |

Statistical analysis was performed using Student’s t test.
as a routine part of the patient condition, so that there is a low prevalence in retrospective studies, necessitating the implementation of prospective studies so that an accurate incidence of such ADRs can be known.

The data presented in this paper demonstrate that the adverse reactions to vancomycin remain a serious public health problem, even after five decades of its inclusion in antimicrobial therapy.

Taking into account the methodological differences and characteristics of each population in previous studies, it can be seen that the ability to control the occurrences of these adverse reactions has not evolved much during the last 20 years.

Conclusions

Despite the limitations of this study design, small sample size and period of realization (2003-2004), especially regarding the generalization of the results, this study allowed a profile to be drawn showing the reality of the use of vancomycin in a quaternary university hospital with high demand. In assessing the prevalence of adverse reactions to vancomycin it was possible to show that it is still the case that many are not even perceived and even less reported. A larger study, including a more diverse study sample, is necessary in order to replicate the findings and overcome the limitations of the present study. It is also necessary to conduct a multiple variable analysis [31] to disclose the possible interrelations between the different exposure variables pointed by this study, becoming possible to select groups of patients whose vancomycin treatment should be more carefully monitored. Despite the occurrence of ADRs due to vancomycin use, it is an indispensable antibiotic to treat a broad type of severe infections. However the healthcare professionals should be aware of the possibility of vancomycin ADR, emphasizing the importance of pharmacovigilance activities, including an active search for adverse reactions.

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Authors’ contributions

DSM contributed to the data collection process and contributed to the writing of the manuscript. MGRS contributed to the data collection. BLAF contributed to the data analysis process. HC and CRR participated in the work coordination and helped to draft the manuscript. VPS and LMC designed the study, supervised data collection, contributed to data interpretation, and critically revised the manuscript for intellectual content. All authors approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

1. Farber BB. Vancomycin: Renewed interest in an old drug. Eur J Clin Microbiol 1984, 3:1.
2. Farber B, Möllering RC. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. Antimicrob Agents Chemother 1983, 23:138-141.
3. Zenon GJ, Cadle RM, Hamill RJ. Vancomycin-induced thrombocytopenia. Arch Intern Med 1991, 151:995-996.
4. Shah RA, Musthaq A, Khardori N. Vancomycin-induced thrombocytopenia in a 60-year-old man: a case report. J Med Case Reports 2009, 3:7296-7294.
5. Vidal C, Gonzalez Quintela A, Fuente R. Toxic epidermal necrolysis due to vancomycin. Ann Allergy 1992, 68:134-347.
6. Banche SE, Dust WN, Sheehan K. Vancomycin-induced neutropenia resolves after substitution with teicoplanin. Clin Infect Dis 2000, 31:822-825.
7. Rocha JL, Kondo W, Baptista MI, Da Cunha CA, Martins LT. Uncommon vancomycin: induced side effects. Braz J Infec Dis 2002, 6:195-200.
8. Bailey P, Gray H. An elderly woman with ‘Red Man Syndrome’ in association with oral vancomycin therapy: a case report. Cases J 2008, 1:111-113.
9. Gilman A, Limbird L, Hardman J. Goodman & Gilman’s: The Pharmacological Basis of Therapeutics. New York: McGraw-Hill Professional; 2001.
10. Wallace MR, Mascola JR, Oldfield EC. Red man syndrome: incidence, etiology, and prophylaxis. J Infect Dis 1991, 164:1180-1185.
11. Zanella RC, Lima MDJC, Tegani LS, Hitomi A, Brandileone MCC, Palazzo KV, et al. Emergence of VanB phenotype-vanA genotype in vancomycin resistant enterococci in Brazilian hospital. Braz J Microbiol 2006, 37:117-118.
12. Světrály S, Lebovici L, Paul M. The comparative efficacy and safety of vancomycin vs. teicoplanin: Systematic review and meta-analysis. Antimicrob Agents Chemother 2009, 53:4069-4079.

Table 4 Characteristics of patients that did and did not presented adverse drug reactions (ADRs)

| Characteristics          | Patients ADR + | Patients ADR - |
|--------------------------|----------------|----------------|
| Age (years)              | Median 47      | Median 49.1    |
|                          | Mean 49.1      | Mean 42.0 - 56.3 |
| Treatment time (days)    | Median 7.0     | Median 11.6    |
|                          | Mean 11.6      | Mean 7.7 - 15.5 |
| Total Vancomycin dose (g) | Median 8.0    | Median 23.3    |
|                          | Mean 23.3      | Mean 6.5 - 40.1 |
| Vancomycin Daily dose (g/day) | Median 1.4 | Median 2.0     |
|                          | Mean 2.0       | Mean 1.1 - 2.8 |
| Initial creatinine (mg/dl)| Median 1.1     | Median 1.7     |
|                          | Mean 1.7       | Mean 1.1 - 2.3 |
| Albumin (g/dl)           | Median 1.4     | Median 1.9     |
|                          | Mean 1.9       | Mean 1.6 - 2.1 |

Statistical analysis was performed using z-test. P > 0.05 for all the parameters evaluated comparing patients ADR + and -.
13. Rybak M, Lomaestro B, Rotschafer JC, Moellerin R, Craig W, Billeter M, et al: Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009, 66:82-98.

14. Karch FE, Lasagna L. Adverse drug reactions: A critical review. JAMA 1975, 234:1236-1241.

15. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981, 30:239-245.

16. Naranjo CA, Shear NH, Busto U. Adverse drug reactions. In Principles of medical pharmacology. 6th edition. Edited by: Kalant H, Roschlau WHE. Oxford University Press: New York; 1998:791-800.

17. Vance-Bryan K, Rotschafer JC, Gilliland SS, Rodvold KA, Fitzgerald CM, Guay DRP. A comparative assessment of vancomycin-associated nephrotoxicity in the young versus the elderly hospitalized patient. J Antimicrob Chemother 1994, 33:811-821.

18. Goetz MB, Sayers J. Nephrotoxicity of vancomycin and aminoglycoside therapy separately and in combination. J Antimicrob Chemother 1993, 32:325-334.

19. Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. J Antimicrob Chemother 1990, 25:679-687.

20. Healy DP, Sahai JV, Fuller SH, Polk RE. Vancomycin-Induced histamine release and "red man syndrome": comparison of 1- and 2-hour infusions. Antimicrob Agents Chemother 1990, 34:550-554.

21. Castro LLC. Fundamentos de Farmacoepidemiologia Sao Paulo: Grupuram; 2000.

22. Bauer L. Applied Clinical Pharmacokinetics New York: McGraw-Hill Medical; 2001.

23. Rybak MJ, Bailey EM, Warbasse LH. Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. Antimicrob Agents Chemother 1992, 36:1204-1207.

24. Finch RG, Eliopoulos GM. Safety and efficacy of glycopeptide antibiotics. J Antimicrob Chemother 2005, 55:i5-i13.

25. Hing WC, Bek SJ, Lin RT, Li SC. A retrospective drug utilization evaluation of vancomycin usage in paediatric patients. J Clin Pharm Ther 2004, 29:359-365.

26. Von DA, Curtis BR, Bougie DW, McFarland JG, AHI S, Limbu I, et al. Vancomycin-induced immune thrombocytopenia. N Engl J Med 2007, 356:904-910.

27. Beringer PM, Wong-Beringer A, Rho JP. Economic aspects of antibacterial adverse effects. Pharmacoecon 1998, 13:35-49.

28. Sahai J, Healy DP, Garris R, Berry A, Polk RE. Influence of antihistamine pretreatment on vancomycin-induced red-man syndrome. J Infect Dis 1989, 160:876-881.

29. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976, 16:31-41.

30. Beringer PM, Wong-Beringer A, Rho JP. Predictive performance of a vancomycin-aminoglycoside population model. Ann Pharmacother 1998, 32:176-181.

31. Maldonado FH. Multivariate analysis used in the investigation of antimicrobials. Revista espanola de quimioterapia publicacion oficial de la Sociedad Espanola de Quimioterapia 2007, 20:300-309.

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