Pinnacle Medicine & Medical Sciences (ISSN: 2360-9516)

http:/www.pjpub.org

Research Article **Vol. 2 (6), 2015.**

Vancomycin-Related Problems In Hemodialysis

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Accepted 30 June, 2015.

ABSTRACT

Introduction: Vancomycin is a glycopeptide antimicrobial and is regarded as the drug of first choice for the treatment of *Methicillin-ResistantSstaphylococcus aureus* (MRSA) infections. This antimicrobial is commonly prescribed for infection treatment in dialysis centres. **Objective:** The aim of this study is to identify vancomycin related problems, including inappropriate doses and mismonitoring, as well as to establish the associations between vancomycin related problems and hemodialysis patient outcomes (recovery or death), in a University Hospital. **Methods:** A retrospective cross sectional study was carried out with 15 stage 5 Chronic Kidney Disease patients on low-flux hemodialysis and on vancomycin treatment (1 gram per dose). Vancomycin doses were evaluated according to the literature recommendations. Vancomycin troughs were evaluated in order to verify whether vancomycin level was within the therapeutic range. Patients were classified into two groups according to the outcome (recovery or death). Statistical analyses were performed in order to identify whether misdosing and mismonitoring were associated to patient outcome. **Results:** All patients underwent vancomycin inadequate dose in, at least, one moment during the hospital stay. Troughs were out of renge in 68.8% of blood samples (p = 0.0004). Multi-resistant microorganisms were identified in six patients who died (p= 0.0002). **Conclusions:** It isimperative to prescribe vancomycin correctly, based upon the patient actual body weight. In addition, it is also important to monitor this antimicrobial adequately. Gram-negative double coverage is also strongly recommended in settings in which MDR microorganisms are identified.

Keywords: vancomycin, therapeutic monitoring, hemodialysis, gram-negative co-infection.

Introduction

Vancomycin is a glycopeptide antimicrobial and is regarded as the drug of first choice for the treatment of *Methicillin-ResistantSstaphylococcus aureus* (MRSA) infections (Mohr & Murray, 2007; Rybak *et al*., 2009).

Vancomycin is considered a broad spectrum antimicrobial with action against gram-positive bacteria (*Staphylococci* and *Streptococci*), as well as some strains of *Chlostridium, Actinomyces, Listeria* and *Enterococcus* (Levine, 2006; Micromedex, 2014).

In the late 80's, some strains of vancomycin-resistant enterococcus (VRE) were identified (Murray *et al.*, 1997) and, in the 90's, vancomycin intermediately resistant *Sstaphylococcus aureus* (VISA) (Hiramatsu, 1991) was identified. Subsequently, Johnson (1998) and Ploy (1998) identified *Vancomycin Resistant Staphylococcus aureus* (VRSA). The emergence of vancomycin resistant strains led to the study of this phenomenon and the identification of its biological underpinnings. According to Sakoulas and colleagues (*Sakoulas et al.*, 2006), *Staphylococcus aureus* (*S. aureus*) exposure to low vancomcyin serum levels contributes directly to the selection of resistant strains. Serum levels below 10 mg/liter are a therapeutic failure and increase the likelihood of VISA outbreaks (Sakoulas *et al*., 2006). Kullar and colleagues showed that a vancomycin trough below 10 mg/liter correlates with treatment failure (Kullar *et al*., 2011a).

It is therefore strongly recommended that vancomycin serum levels are maintained above 10 mg/liter for the treatment of non-complicated infections (Rybak *et al*., 2009). Vancomycin resistance is related to its mechanism of action, which occurs via the inhibition of cell wall synthesis (Micromedex, 2014). Resistant strains are able to replace the amino acid residues required for vancomycin to bind to the to cell wall. More specifically, resistant strains can replace alanine for serine, thereby blocking vancomycin's action (Micromedex, 2014).

Pharmacokinetically, vancomycin is a 1.49-kDa drug that is poorly absorbed by the gastrointestinal tract as well as being poorly metabolized (30%). Its solubility in water is low (distribution volume = 0.6 l/kg), although 90% of vancomycin is naturally eliminated in the urine (Dollery, 1999). In patients with normal renal function, the vancomycin elimination half-life is 5-11 hours (Micromedex, 2014), with elimination time being increased in renal failure patients, some of whom may show a half-life of 7-12 days (Chambers, 2006). This necessitates the need for careful monitoring and dose adjustments in these patients (Frye e Matzke, 2005). Vancomycin is also potentially nephrotoxic, with this adverse drug reaction (ADR) estimated to occur in 7 to 17 % of hospitalized patients (Downs et al., 1989; Emg et al., 1989; Mellor, 1985), and therefore requires careful monitoring of vancomycin levels and renal function (Rybak *et al.*, 2009; Kullar *et al*., 2011a). The incidence of vancomycin-induced nephrotoxicity may be significantly increased by the adjunctive use of other drugs, including piperacillin-tazobactam, aminoglycosides and dry-contrast (Kullar *et al*., 2011a).

The mechanism(s) of vancomycin-induced nephrotoxicity has still to be fully clarified. Oxidative stress and reactive oxygen species (ROS) generation at least partly mediate vancomycin-induced renal damage in the proximal tubule (Elyasi *et al*., 2012).

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The imminence of future resistant strains requires close therapeutic monitoring (Rybak *et al*., 2009; Kullar *et al*., 2011a). Rybak and colleagues recommend vancomycin troughs above 10 µg/ml during treatment of non-complicated *S. aureus* infections, with troughs of between 15 to 20 µg/mL in the case of more severe infections (Rybak *et al*., 2009). Due to concerns about bacterial resistance and dose adjustments, vancomycin treatment is complex in renal patients, with this further complicated by vancomycin elimination during hemodialysis treatment (Barth & DeVicenzo, 1996; Stamatakis *et al*., 2003; Trotman *et al*., 2005). Overall, the imminence of resistant strain outbreaks, the complexity of renal patient presentations, vancomycin loss during hemodialysis and the risk of therapeutic failure make research on vancomycin treatment in renal patients an important area of investigation. In some countries, including Brazil, the regulatory authority has expressed concerns about vancomycin use (Soriano *et al*., 2008; ANVISA, 2010). Consequently, we evaluated the vancomycin use profile in hemodialysis patients at the São Paulo University Hospital.

Objective

The aim of this study is to identify vancomycin related problems, including inappropriate doses and mismonitoring, as well as to establish the association between vancomycin related problems and hemodialysis patient outcomes (recovery or death), in a University Hospital.

Materials and Methods

Study Classification: A retrospective cross sectional study was carried out between December 2008 and December 2010. **Patients - *Inclusion criteria*:** Male and female patients aged 21 year-old and above, on vancomycin treatment (dose number >=3) and on low flux hemodialysis (session number >= 3) due to a kidney disease were considered eligible for this study. ***Exclusion criteria*:** Pregnant and burned patients were not included. **Hemodialysis Parameters - *Hemodialysis Classification*:** Low-flux hemodialysis. ***Time Session*:** 4-hour session, three times a week. ***Dialyser*:** F8. ***Blood Flow*:** 300 mL/min. ***Dialysate Flow*:** 400 mL/min. ***Kt/V*:** calculated according to the parameters established by the guidelines (KDOQI, *Kidney Disease Outcomes Quality Initiative*). **Treatment Data - *Dosage Form*:** Solution, reconstituted intravenous, 1 gram (1 ea). ***Vancomycin Dosing*:** patients were treated with 1 gram of vancomycin, administered at the end of the hemodialysis session. Supplemental doses of 1 gram were administered when it was needed. ***Administration*:** intermittent i.v. infusion over 60 minutes. Vancomycin solution concentration of 5 mg/ml (in NS 0.9%), administered within the recommended infusion period of 30 minutes for every 500 mg of vancomycin. **Vancomycin Monitoring - *Laboratory Assay*:** vancomycin levels were monitored using a fluorescence polarization immunoassay, Abbott AxSym System Vancomycin II (Abbott, IL, USA). Vancomycin levels were determined at the trough. Pharmacokinetics Assessment (PkA): PkA was not assessed due to insufficient data on peak levels. Only data pertaining to troughs were sufficient to draw serum concentration curves.

Study Design

Demographic and clinical characteristics were obtained from medical records, medical appointments and computerized systems. Sex, race, age, body weight, indication for vancomycin use and treatment period were determined. Patients were divided into two groups, according to outcome: Group R, patients who recovered after vancomycin treatment and at the end of the hospital stay; Group D, patients who died after vancomycin treatment and the end of the hospital stay. One-gram vancomycin doses were prescribed to renal patients at this hospital and they were compared to the loading dose (25-30 mg/kg) and maintenance dose (15-20 mg/kg), as recommended2. For this comparison, the one-gram vancomycin doses were divided by patient actual body weight. The vancomycin troughs were also compared to previous data pertaining to this (Rybak *et al*., 2009; Kullar *et al*., 2011b).

Statistical analysis - *Descriptive Analysis*: Median and standard deviations were obtained for continuous variables. Frequency and percentage were determined for categorical variables. ***Comparative Analysis*:** A probability value of $p \leq 0,05$ was considered significant. Fisher's Test, Binomial Test and T-student test were used for statistical comparison, according to the variable type.

Results

From December 2008 to December 2010, 15 patients on low-flux hemodialysis and receiving vancomycin doses of 1 gram, were considered eligible and studied according to the inclusion criteria.

The demographic and clinical characteristics of patients are shown in Table 1. Both groups are regarded as homogeneous for sex, age, race, weight and infectious disease (p-value >0.05). The median age was 53.97±13.13 years and median weight was 75.1±12.22 kg. Severe infections were diagnosed in all patients (septic shock or hospital-acquired infections). The median treatment period for all included patients was 12.8±5.58 days. Comparing groups R and D for treatment period showed a significant difference (p = 0.0182) between group D (9.17±2.64 days) and group R (15.2±5.80 days).

There was no significant difference (p = 0.3826) in the prescribed doses between groups D (13.0±1.67) and R (14.02±2.28 mg/kg).

Table 2 shows the number of patients with right and wrong prescribed loading doses, as well as right and wrong maintenance doses, for both groups. For both groups the loading dose was wrong for all patients. In both groups, the percentages of right and wrong maintenance doses were similar (p-value = 0.5804).

Table 3 shows the number and percentage of vancomycin serum levels at the troughs within the range (15-20 mg/liter) and out of this range, considering all patients. The percentage of troughs within this range (31.2%) was significantly lower (p = 0.0004) than the percentage outwith this range (68.8%).

Table 4 shows the microorganisms identified in groups D and R. There was no difference in *S. aureus* detection between groups (p = 0.5804). However, a significant difference was

identified between the groups for multi-resistant microorganisms (p = 0.0002), being only evident in 6 group D patients. The microorganism, *Acinetobacter baumanii*, was present in 4 patients and *Stenotrophomonas* in 2 patients.

Discussion

This study presents relevant clinical findings. Firstly, this paper addresses concerns regarding the adequacy of vancomycin doses for the treatment of severe infections.

The patient sample was homogeneous between groups for sex, age, race, weight and prescribed vancomycin dose (p >0.05). However, the treatment period was significantly lower in Group D (p = 0.0182) due to the identification of multi-resistant microorganisms in this group, which led to a change in pharmacotherapy and the discontinuation of vancomycin treatment. It was found that the 1 gram of vancomcyin prescribed in this study was equivalent to a mean dose of 13.0±1.67 mg/kg in group D and 14.02±2.28 mg/kg in group R. These doses are lower than recommended for the treatment of severe infections (Rybak *et al*., 2009). This practice of underprescribing was evident in both groups (p-value = 0.3846).

As a result, the prescribed doses were not sufficient to maintain vancomycin troughs between 15 and 20 mg/liter, with the percentage of vancomycin troughs outwith (68.8%) versus within (31.2%) this range, being highly significant (p = 0.0004).

These two results, namely: lower than the recommended doses and vancomycin troughs outwith the range, highlight the need to adopt recommendations regarding loading (25-30 mg/kg) and maintenance (15-20 mg/kg) doses during vancomycin treatment (Rybak *et al*., 2009). As such, the present data reinforces the need for vancomycin prescribing that is based upon actual body weight (ABW).

Critically ill patients who have complicated infections and are on hemodialysis should receive loading doses of 25-30 mg/kg, followed by appropriate maintenance doses. Patients on hemodialysis, but with non-complicated infections should receive an initial dose of 15-20 mg/kg. The vancomycin supplemental doses of 7.5 mg/kg, administered during the last hour of the hemodialysis session, must take into account the trough level, which should be obtained every 48 hours. Another factor that contributes to the large number of vancomycin troughs out with the recommended range is hemodialysis treatment *per se*. Both, low-flux and high-flux hemodialysis lead to vancomycin loss, emphasizing the need for prescribing according to ABW and for appropriate vancomycin supplemental doses during the last hour of hemodialysis (Barth & DeVicenzo 1996; Stamatakis *et al*., 2003).

Ibrahim and colleagues (2000) evaluated the correlation between the adequacy of antimicrobial therapy for blood stream infection and clinical outcome in intensive care units (Ibrahim *et al*., 2000). In that study, 492 patients (29.9%) received an inadequate antimicrobial therapy. The hospital mortality rate among patients who experienced systemic infection, whilst under inadequate antimicrobial therapy was statistically higher (61.9%) than the mortality rate of patients who experienced systemic infection under adequate antimicrobial therapy (28.4%) (Ibrahim *et al*., 2000). The present data also show a high association of multi-resistant microorganisms with patient death in group D (p = 0.002), highlighting the importance of multi-resistant microorganisms to patient fatality. It should be emphasized that inadequate antimicrobial therapy is a risk factor for multi-resistant microorganisms, with *acinetobacter baumanii,* identified in this study in 4 patients, leading to patient death. Jung and colleagues (2010) highlighted risk factors related to *Acinetobacter baumanii* infections, including severity of clinical status, previous MRSA infection, renal injury and previous antimicrobial therapy (Jung *et al*., 2010). The patients in that study were exposed to many mortality risk factors, including kidney disease, hemodialysis, long-term hospital stay and *S. aureus* infections (Jung *et al*., 2010). These risk factors were also evident in this study, with the high mortality rate (40%) driven by secondary infections, highlighting the clinical relevance of this work. Because of the high prevalence of gram-negative bacteria leading to mortality, we strongly recommend double coverage for gram negative microorganisms, including coverage for microorganisms like *Acinetobacter baumanii, Pseudomaonas aeroginosa, Serratia marcescens, Stenotrpphomonas maliophilia* and *Klebsiella sp ESBL*. Other health care institutions around the world may be struggling to kill these bacteria and, therefore, the double coverage for gram-negative microorganisms is strongly recommended.

Conclusions

Although comprising a small patient sample, this study highlights important points in the course of prescribing and monitoring vancomycin. In order to achieve the best patient therapeutic outcome, it is imperative to prescribe vancomycin adequately, based upon actual body weight. Furthermore, it is important to provide antimicrobial treatment with adequate coverage for gram-negative strains. An effective antimicrobial stewardship programme is a growing imperative for health care settings.

The vancomycin-related problems explored in this article may be occurring in other centres as well as the occurrence of MDR microorganisms. Gram-negative double coverage is also strongly recommended in settings in which MDR microorganisms are identified.

Our data has relevance to everyday clinical protocols that should increase patient safety and survival, as well as the general quality of health care.

Acknowledgments:

The present study was part of the M.Sc. dissertation of M. V. S. João-Luiz, who received a fellowship from CNPq. Research supported by grants from The University of São Paulo (USP). We also thank Dr. Bruce Mueller (University of Michigan, College of Pharmacy) and Dr. Amit Pai (Albany College of Pharmacy and Health Sciences) for many contributions in this article.

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How to Cite this Article: Marcus Vinicius de Souza João Luiz, Cristoforo Scavone, Moacyr Luiz Aizenstein "Vancomycin-Related Problems In Hemodialysis" Pinnacle Medicine & Medical Sciences ISSN: 2360-9516, Vol. 2 (6), 2015, Article ID pmms_204, 771-776, 2015.

Tables

Characteristic	Group D	Group R	All Patients	p-value
Gender				
Male	5 (83.3%)	5 (55.6%)	10 (67.7%)	0.5804
Female	1 (16.7%)	4 (44.4%)	5 (33.3%)	
Total	6	9	15	
Age (years)	57.27±16.34	51.78±11.02	53.97±13,13	0.4483
Race				
White	3 (50.0%)	6 (66.7%)	9 (60%)	0.6224
Black	3 (50.0%)	3 (33.3%)	6 (40%)	
Total	6	9	15	
Weight (kg)	77.87±10.83	73.26±13.37	75,1 ± 12,22	0·4946
Infectious Disease				
Severe Infection	6 (100.0%)	9 (100.0%)	15 (100.0%)	Not calculated
Total	6	9	15	
Treatment Period (days)	9.17±2.64	15.22±5,80	12.8±5.58	**0·0182***
Prescribed dose (mg/kg)	13.03±1.67	15.22±5,80	13.62±2.06	0·3846

Table 1: Demographic and Clinical characteristics of the study patients.
Legend - Group D: patients who died at the end of hospital stay. Group : group of patients who recovered at the end of hospital stay. M (mean). SD (Standard Deviation); HAP (Hospital-Acquired Pneumonia); Transference: patient was transferred to other hospital. Treatment Period: period on vancomycin treatment. Gender, expressed in number and percentage, Age, expressed in M (SD) years. Weight, expressed in M (SD) kg. Treatment Period, expressed in M (SD) days. Prescribed dose, expressed in M (SD) mg/kg. Infectious Disease - Severe Infection: number of patients diagnosed with severe infection which required vancomycin use.

Dose	Outcome		
	Recovery n (%)	Death n (%)	p-value**
Loading			
Right	0 (0.0%)	0 (0.0%)	Not calculated
Wrong	9 (100.0%)	6 (100.0%)	
Total	9	6	
Maintenance			
Right	4 (44.4%)	1 (16.7%)	0.5804
Wrong	5 (55.6%)	5 (83.3%)	
Total	9	6	

T**able 2:** Dose Classification according to the level range.
Legend: Recovery: group of patients who recovered at the end of length of hospital stay. Death: group of patients who died at the end of the hospital stay. n: indicates the number of patients. %: indicates the percentage of patients. Loading: indicates loading dose preconized in the literature (25-30 mg/kg). Mauntenance: indicates maintenance dose preconized in the literature (15-20 mg/kg). Right indicates that corrected dose was prescribed to the patuent. Right: indicates that the vancomycin dose is correct. Worng: indicates that the vancomycin dose is incorrect. ** Fisher's Test. Confidence interval: 95%.

Level range	Result		
	number	percentage	p-value**
Range	29	31.2%	**0.0004**
Out of range	64	68.8%	
Total	93	100%	

Table 3: Number and percentage of vancomycin troughs according level range.
Legend - range: therapeutic vancomycin trough, between 15 and 20 µg/ml. out of range: indicates the vanvomycin trough is below 15 to 20 µg/ml or above 15 to 20 µg/ml. * Binomial Test. Confidence interval: 95%

Microorganism	Outcome		p-value**
	Recovery	Death	
***S. aureus* n (%)**			
Yes	4 (44.4%)	1 (16.7%)	0.5804
No	5 (55.6%)	5 (83.3%)	
Total	9	6	
Multi-Drug Resistant n (%)			
Yes	0 (0.0%)	6 (100.0%)	**0.0002**
No	9 (100.0%)	0 (0.0%)	
Total	9	6	

Table 4: Identified microrganism.
Legend - *S. aureus: Staphyloccocus aureus.* Multi-Drug Resistant: multi-drug resistant microorganism. n: number of patients. (%): percentage of patients. ** Fisher's Test. Confidence interval: 95%