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ORIGINAL ARTICLE

Therapeutic Drug Monitoring (TDM) based precise doing of Vancomycin in Intermittent Hemodialysis (IHD) patients

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ABSTRACT

Aim: To find out the precise dosing of vancomycin in intermittent haemodialysis patients to overcome persistent sub-therapeutic levels so that methicillin resistant S. aureus infections can be avoided.
Methods: Total 167 patients were subjected to this study, and their serum vancomycin trough profiles were assessed accordingly. The patients were divided according to gender and age subgroups. Three dose levels, such as 1 g, 1.5 g, and 2 g of vancomycin, were administered, and their trough level was monitored. All the data were subjected to one-way ANOVA (analysis of variance) by SPSS analytical software, and Tukey's test was applied for means significance.
Results: It had been revealed that few patients attained trough level with the administration of 1 g (1st dose) of vancomycin. Similarly, the patients who didn't attain the maximum trough level post 1 mg administration achieved the maximum trough level after 1.5 g (2nd dose) and 2 g (3rd dose) administration of vancomycin, respectively. A non-significant difference was observed among male and female patients attaining the maximum trough level post 1st, 2nd, and 3rd dose levels of vancomycin. Similarly, a non-significant difference was also observed in different age groups of patients attaining the maximum trough level post 1st, 2nd, and 3rd dose levels of vancomycin. These results showed that therapeutic drug monitoring is an effective way for achieving optimum levels to get the desired response.
Conclusion: Patients were found to have sub-therapeutic levels of vancomycin. They were required at least three subsequently upgraded doses to attain therapeutic levels to avoid methicillin-resistant S. aureus infections.
Keywords: Therapeutic drug monitoring, Vancomycin, Intermittent hemodialysis, sub-therapeutic

INTRODUCTION

Patients receiving intermittent haemodialysis (IHD) have a tendency to develop infections, mostly as a result of vascular access, which is proven to be a second leading cause of death. Among pathogens, Staphylococcus aureus is a well-known cause of infections in patients receiving IHD, comprising 27% to 39% of all cases of bacteremia.Such people have a 100-fold higher probability of experiencing invasive methicillin-resistant *S. aureus* (MRSA) than the general population. In these circumstances, Vancomycin has proven to be an ideal choice for combating such infections. By nature, Vancomycin is a glycopeptide antibiotic that plays its role against infections produced by S. aureus, Staphylococci, and other gram-positive organisms. Although it is well known for its narrow therapeutic window and dosing complexity, it's still widely used in clinical practice[1].

Usually, 80 to 90% of the vancomycin is excreted unaffected within 24 hours in the urine of patients with normal renal function after single-dose administration. In cases of dysfunctional kidney systems, clearance of vancomycin is compromised and must be adjusted either with dose reduction or an increase time interval. As it is known that vancomycin belongs to the class of narrow therapeutic drugs, there is a dire need to carry out therapeutic drug monitoring (TDM) to avoid unwanted adverse reactions as a consequence of over-dose exposure or response failure associated with an under-dose regimen[2-5].

Chronic kidney disease: The most severe result of chronic kidney disease is widely thought to be renal failure, and symptoms are typically brought on by side effects of impaired kidney function (Fig. 1). A glomerular filtration rate (GFR) of less than 15 mL/min per 1.73 m^2, the requirement for dialysis or transplantation, or both, are considered signs of kidney failure. Complications of low GFR include increased risk of cardiovascular disease, acute renal injury, infection, cognitive decline, and poor physical function, among other outcomes. Complications can develop at any point, can result from adverse events, and frequently result in mortality without progression to renal failure[6-8].

The objective of the study was to find out precise dosing of vancomycin in intermittent haemodialysis patients to overcome persistent subtherapeutic levels so that methicillin resistant S. aureus infections can be avoided.

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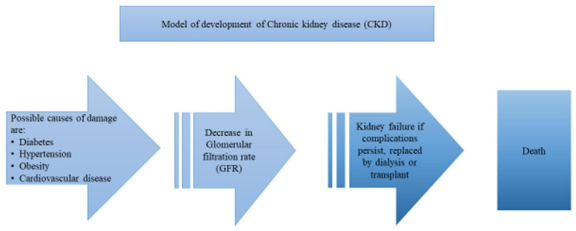
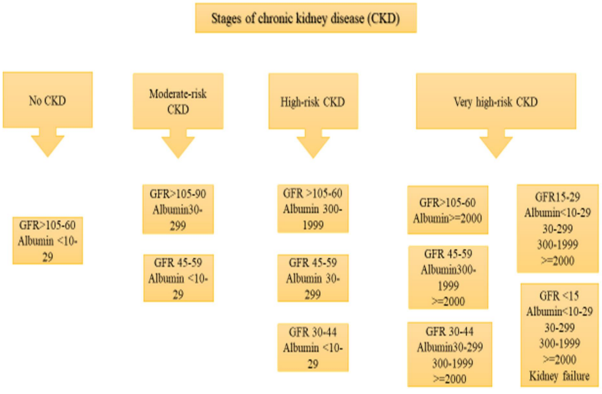
Figure 1: Model of development of chronic disease



According to results from both experimental and clinical research, proteinuria plays a significant role in the aetiology of illness development. In addition to low GFR and cardiovascular disease risk factors, epidemiological studies have found graded relationships between elevated albuminuria and mortality and kidney outcomes in a variety of study groups. An international meeting suggested changing disease categorisation to include stages based on albuminuria in order to predict prognosis, as shown in Fig. 2[6-8].

Figure 2: GFR and Albuminuria based CKD prognosis



The studies were carried out to evaluate the dosing pattern at which optimum levels of vancomycin (15 to 20 mg/L) can be achieved. After execution of the drug protocol, every kidney patient received a 1st loading drug dose at the rate of 1000 mg, 1500 mg, or 2000 mg and a drug maintenance dose at the rate of 500 mg, 750 mg, or 1000 mg, all dependent on patient body weight. The percentage of vancomycin blood serum concentration among 10 mg/L and 22 mg/L was greater in the patient treatment with a pre-3rd intermittent hemodialysis by use of drug protocol than with traditional care. At the research institution, they reached the recommended vancomycin drug blood serum concentration after using the vancomycin drug dosing protocol for intermittent haemodialysis patients.[9-13]

MATERIAL AND METHODS

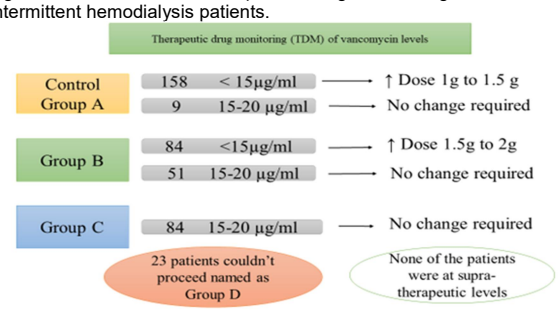
A cross-sectional study was conducted at the dialysis center of Al-Shifa International Hospital Faisalabad. 167 patients were selected according to the established criteria of the study. All patients were scheduled for intermittent hemodialysis (IHD) as under:

First dialysis day/ week	Second dialysis day/week
Monday	Thursday
Tuesday	Friday
Wednesday	Saturday
Thursday	Sunday

Intermittent dialysis was done with a 300 ml/min blood flow rate and a 500 ml/min dialysis flow rate. Machine temperature was 37C with conductivity 14.4. Dialysis duration lasts for 4:00 hour given. Vancomycin 1 g injection was given in an infusion vial of 0.9% NaCl solution 100 ml over 45 minutes post dialysis. Caution was taken not to administer a vancomycin infusion less than 45 minutes.

The first dose of vancomycin was administered after the first completion of the first session of hemodialysis. The blood samples were drawn just before the start of the second session of dialysis. Then blood samples were sent to the laboratory for vancomycin C trough concentration analysis by the Rosch vancomycin kit. The kit works on a principle that is based on the kinetic interaction of microparticles in a solution (KIMS). The process carried out process is as follows (Figure 3).

Figure 3: Process of Therapeutic drug monitoring of vancomycin in Intermittent hemodialysis patients.



RESULTS

Results have shown a gradual increase in vancomycin through levels following an increase in doses.In addition, based on gender, a non-significant difference ($p<0.05$) was observed between male and female patients attaining the maximum trough levels subsequent an increase in doses. Similarly, a non-significant difference ($p<0.05$) was observed between age groups such as 30 to 45 years, 46 to 60 years, and 61 to 75 years old patients attaining the maximum trough level as shown in table 1.

Table 1: Gender and age-based trough levels of vancomycin after 1st, 2nd,3rd doses who achieved therapeutic levels

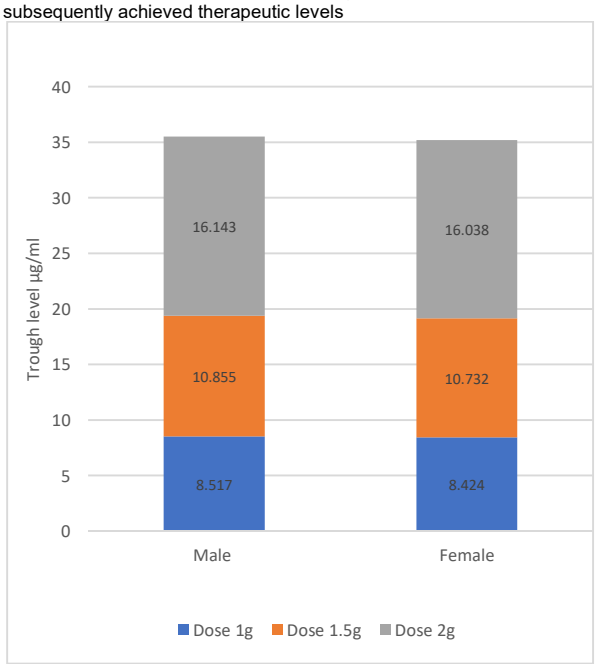
Dose	Trough level (Mean ± SD)
1st dose (1g) of vancomycin	
Gender	
Male	15.617 ± 0.243a
Female	15.321 ± 0.232a
Age	
30 – 45 years	15.63 ± 0.243a
46 – 60 years	15.184 ± 0.232a
61 – 75 years	15.834 ± 0.232a
2nd dose (1.5g) of vancomycin	
Gender	
Male	15.767 ± 0.669a
Female	15.632 ± 0.532a
Age	
30 – 45 years	15.858 ± 0.741a
46 – 60 years	15.767 ± 0.669a
61 – 75 years	15.632 ± 0.532a
3rd dose (2g) of vancomycin	
Gender	
Male	16.143 ± 0.607a
Female	16.038 ± 0.653a
Age	
30 – 45 years	16.033 ± 0.678a
46 – 60 years	16.043 ± 0.639a
61 – 75 years	16.075 ± 0.691a

Table 2 is showing the gradual increase in therapeutic levels following an increase in dose.

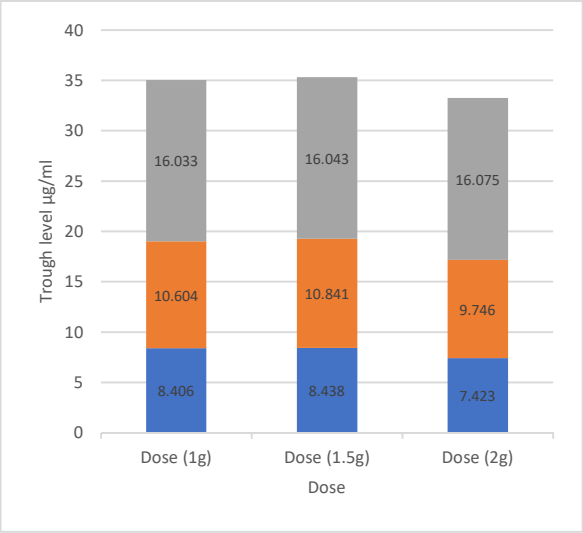
Table 2: Comparison between trough levels of 1st, 2nd, 3rd doses who subsequently achieved therapeutic levels

	1st dose (1g) Trough level (Mean ± SD)	2nd dose (1.5g) Trough level (Mean ± SD)	3rd dose (2g) Trough level (Mean ± SD)
Gender			
Male	8.517±1.912c	10.855±1.796b	16.143 ± 0.607a
Female	8.424±1.852c	10.732±1.798b	16.038 ± 0.653a
Age			
30–45 yrs	8.406±1.773c	10.604±1.813b	16.033 ± 0.678a
46–60 yrs	8.438±1.936c	10.841±1.800b	16.043 ± 0.639a
61–75 yrs	7.423±0.980c	9.746±1.013b	16.075 ± 0.691a

Gender based comparison between trough levels of 1st, 2nd, 3rd doses who subsequently achieved therapeutic levels



Age-based comparison between trough levels of 1st, 2nd, 3rd doses who subsequently achieved therapeutic levels



DISCUSSION

According to the research, there is a lot of variety in the prescription of the antibiotic vancomycin in prolonged hemodialysis patients, and the used dosages are frequently insufficient, probably leading to sub therapeutic concentrations[12-14]. This research related to our research: in order to reduce the dangers of resistance and the costs to the healthcare system, it is crucial to clarify the clinical practice of vancomycin administration, including therapeutic drug monitoring (TDM), and improve every aspect of its therapy. [12-14] To increase the success rate of treating severe infections where vancomycin is used as the last resort, solutions to improve all factors affecting successful vancomycin therapy, including TDM therapeutic drug monitoring (initial dosing, appropriate timing of blood sampling, target concentration, and their interpretation), must be put into practice. There have been numerous attempts to publish standardized recommendations in various nations that address the complexities of vancomycin dose and therapeutic drug monitoring (TDM), but there are still many questions about how to put these recommendations into practice successfully[15].

As in our study, after the first dose (1 g) of vancomycin, 9 out of 167 achieved the desired therapeutic level. The remaining 158 patients failed to reach the desired concentration at the start of therapy, which renders them vulnerable to infections. Twenty three patients couldn't pursue the treatment because of financial issues. After enhancing the dose to 1.5 g, only 51 patients have acquired the desired concentration of vancomycin. 84 patients remained sub therapeutic. Then these patients have achieved the desired concentration after an increase in dose to 2 g. Similar to our study, the majority of patients do not reach therapeutic vancomycin serum concentrations during the first few days of therapy or even during vancomycin therapy. According to this research, if the target through concentration of vancomycin is reached within 5 days of the start of vancomycin therapy, the time of discharge and duration of vancomycin therapy may be shortened[16-18].

CONCLUSION

Methicillin-resistant S. aureus (MRSA) infections are posing life-threatening consequences in intermittent hemodialysis patients (IHD). Vancomycin is a lifesaving drug, especially when the vascular system is breached through any form of vascular access according to international protocols. Therapeutic levels of vancomycin are key to the success of treatment and ensuring the survival of patients. In our study, patients took three enhanced doses ranging from 1 g to 2 g to achieve therapeutic levels of vancomycin. Unfortunately, affordability played a vital role; 10 out of 23 patients who couldn't pursue treatment had lost their lives due to severe bacteremia.

Authorship and contribution declaration: Each author of this article fulfilled following Criteria of Authorship:

1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

All authors agree to be responsible for all aspects of their research work.

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