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Is vancomycin monitoring of real value in pediatric cancer patients?

Mohamed S. Imam^{1,2}, Wael Z. Khaled^{1,2}, Mohamed E. A. Abdelrahim^{3,4}, Ahmed A H Ali⁴, Lobna M.E. Shalaby^{1,2}

¹ Pediatric Oncology Department, National Cancer Institute, Cairo University, Egypt

² Pediatric Oncology Department, Children's Cancer Hospital in Egypt

³ Clinical Pharmacy Department, Faculty of Pharmacy, Ahram Canadian University, Giza, Egypt

⁴ Clinical Pharmacy Department, Faculty of Pharmacy, Beni-suef University, Egypt

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Abstract

Vancomycin is not nephrotoxic by itself but many patients using it with other nephrotoxic agents show nephrotoxicity to some extent. Whether to monitor or not to monitor vancomycin needs further study. The aim of the present study was to investigate the significance of monitoring vancomycin serum levels in pediatric patients treated from different malignancies. 150 newly diagnosed pediatric patients, with various types of malignancy treated with different nephrotoxic agents including vancomycin, were recruited in the study. All patients had normal renal functions at the start of the study and were divided into three groups; Group I included 50 (21 females) patients received vancomycin without monitoring (VWOM group); Group II included 50 (19 females) patients received vancomycin with monitoring (VWM group); Group III (Control group) included 50 (23 females) patients received vancomycin-free antimicrobial agents (VF group). Vancomycin trough level was determined only for VWM group. The effectiveness of monitoring was estimated by the ability to achieve more rapid response, decrease hospital stay and nephrotoxicity and its effect on total dose of vancomycin. There was a significant decrease in nephrotoxicity in VWM and VF groups, 9 subjects (18%), compared to 15 subjects (30%) in VWOM group ($p=0.016$). The time needed to show a response achievement was significantly decreased in VWM group compared to VWOM group with mean (SD) of 6.5 (2.5) and 8.7 (3.6) days, respectively ($p=0.015$). That led to shorter hospital stay in VWM group compared to VWOM group with mean (SD) of 10.1 (3.4) and 12.4 (4.2) days, respectively ($p=0.003$). Monitoring vancomycin level was important in the examined high risk groups of pediatric cancer patients studied.

Keywords: Vancomycin; Pediatrics, Therapeutic Drug Monitoring, Neoplasms, Nephrotoxicity, Length Of Hospital Stay

Introduction

Infection leads to major problems in pediatric patients treated from cancer. The chemotherapy regimens may lead to more profound periods of fever and neutropenia. Both gram positive and gram negative bacteria were isolated frequently from the blood in febrile neutropenic children [1,2]. The type and the frequency of pathogenic organisms vary from institution to another. Patients on antineoplastic chemotherapy are often treated with antimicrobial agents, to stop febrile neutropenia. Most of those antimicrobial agents are nephrotoxic such as aminoglycosides and amphotericin B [3,4].

When giving vancomycin as a single agent, which is a drug that is cleared by the kidney, [5] it is associated with a low incidence of nephrotoxicity; however, when it is combined with aminoglycoside antibiotics, the incidence increased to 30% [6-8]. The recommendation to monitor vancomycin was introduced after certain reports about nephrotoxicity in patients who were treated

with vancomycin and other potentially nephrotoxic agents such as aminoglycosides [3,4].

Vancomycin serum trough level monitoring was recommended by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists [9]. They endorsed vancomycin dosing and monitoring guidelines published in 2009.[9] This was predicated on improved efficacy against Methicillin-resistant *Staphylococcus aureus* (MRSA) when an AUC/MIC ratio of 400 is achieved, which correlates with troughs of 10-20 µg/ml for most patients with a vancomycin minimum inhibitory concentration (MIC) less than or equal to 1 mg/L [9].

However, vancomycin dosing and monitoring continues to be controversial in some respects, especially in children [10,11]. With no clear consensus, many clinicians chose to dose according to nomogram data, whereas others measured serum concentrations in every patient [12]. Though, recommendations of monitoring serum levels in certain situations are more practical e.g. when patients receive vancomycin and aminoglycoside combinations [8]; when anephric patients undergoing hemodialysis receive infrequent doses of vancomycin [13]; and when patients receive higher than

*Corresponding Author: Mohamed E. A. Abdelrahim, Associate professor Department of Clinical Pharmacy Faculty of Pharmacy University of Ahram Canadian Egypt, E-mail: mohamedemam9@yahoo.com

usual doses of vancomycin [6,8].

Due to this variation in handling vancomycin monitoring, the aim of the present study was to determine whether the monitoring of vancomycin serum trough levels in pediatric cancer patients with normal renal functions of real importance or not.

Metarial and Methods

The study was performed in one center, the Children's Cancer Hospital in Egypt, 57357, (CCHE). Local hospital research ethics committee approval was obtained. 150 newly diagnosed pediatric cancer patients were recruited in the study. Eligibility criteria of the study population were; age between three months to eighteen years; diagnosed with malignancy; during the period of fever and neutropenia; and started with normal renal functions (i.e. normal serum creatinine level). All patients were recruited using a hospital approved delayed consent procedure.

The study was a randomized controlled trial using SPSS statistical package version 17 (SPSS Inc., Chicago, USA). Patients were divided randomly into three groups: group I included 50 pediatric cancer patients received vancomycin without monitoring (VWOM); group II included 50 pediatric cancer patients received vancomycin with monitoring (VWM) and group III served as control group and included 50 pediatric cancer patients received vancomycin-free antimicrobial agent (VF).

Vancomycin administration method

The initial dose of vancomycin was 15 mg/kg every 6 hours. Vancomycin hydrochloride 1 gram injection, powder, lyophilized, for solution (Mylan institution, USA) was dissolved in 10 ml 0.9% w/v saline (Otsuka Pharmaceutical Group, Egypt) to form a concentrated solution of vancomycin of 10% w/v concentration. The patient calculated dose was withdrawn from this concentrated solution of vancomycin and diluted into 50 ml 0.9% w/v saline. The dilute vancomycin solution was infused to the patient over a 30 minutes period.

Vancomycin monitoring

Patients were monitored by measuring:

(1) Baseline serum creatinine every other day till the end of vancomycin administration using commercially available Beckman® Assay Kits (Beckman Coulter, USA) based on an enzymatic colorimetric determination of creatinine [14]. Nephrotoxicity was defined as an increase in the serum creatinine (SCr) of at least 0.5 mg/dL or a 50% increase in baseline SCr on, at least, two consecutive days [9,15].

(3) The gram positive blood culture was used to assess response of infection to vancomycin. The response achievement was measured

by the period from starting of vancomycin treatment till reaching the first negative blood cultures (no growth).

(3) Vancomycin trough level [9] for VWM group was measured using commercially available Emit® 2000 Vancomycin Assay kits (SIEMENS, Beckman Coulter, USA) using a homogeneous enzyme immunoassay technique.

First trough level was taken for all patients thirty minutes prior to the 4th dose of vancomycin. The levels were classified into; therapeutic levels from 10 µg/ml – 20 µg/ml, sub-therapeutic levels < 10 µg/ml and toxic levels > 20 µg/ml [9]. The doses for patients with sub-therapeutic and toxic serum levels were corrected according to the vancomycin monitoring criteria and Lexi-CALCTM Vancomycin: Dosing by serum levels (Lexi-Comp Inc., Ohio, USA) [16-18]. If needed, another trough level was taken thirty minutes prior to the 8th dose of vancomycin and prior to the 12th dose to check whether the serum level had returned to the therapeutic level or still sub-therapeutic or toxic and need to be corrected. For the patients who continued to receive vancomycin for more than a week, another trough level was taken once weekly. (4) The effectiveness of monitoring was estimated by the ability to achieve more rapid response and to decrease hospital stay and nephrotoxicity and its effect on total dose of vancomycin.

Statistical

Data was analyzed using SPSS statistical package version 17 (SPSS Inc., Chicago, USA). The required total sample size to detect a difference of $p < 0.5$ in the mean of the groups' results was 40 patients per group. Fifty patients in each group were enrolled to account for dropouts. In qualitative data, Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, Mann-Whitney test (non- parametric t-test) was used to compare between two groups. Kruskal-Wallis test (non-parametric ANOVA) was used to compare between the 3 groups then post-Hoc "Scheffe test" on rank of variables was used for pair-wise comparison. Wilcoxon signed-ranks test was used to compare total dose of VWOM group and VWM group.

Results

All patient recruited in the three groups completed the study. Table 1 shows the demographic data and number of patients who developed nephrotoxicity post treatment in the three studied groups. There was no significant difference found in the age, gender distribution and percentage of malignancies type between the three groups. During treatment, significantly more patients in VWOM group developed nephrotoxicity compared to the other two groups ($p = 0.016$).

Table 1. Demographic data and Frequency and percent of nephrotoxicity during treatment in the three studied groups

	VWOM	VWM	VF
Number of females in each group	21	19	23
Mean (SD; range) age in years	6.6 (5.1; 1.0-17.7)	6.9 (4.7; 0.3-16.5)	6.0 (4.2; 0.2-17.7)
Malignancies type (%)			
Hematological	70.0	82.0	69.0
Solid	30.0	18.0	31.0
Frequency and percent of nephrotoxicity during treatment	15 patients (30%)	9 patients (18%)	9 patients (18%)

As shown in Table 2, the mean (SD) total vancomycin doses given to VWM and VWOM groups showed no significant difference. Also, no significant difference was found in the number of patients who had gram positive infection in VWM and VWOM groups. In those patients the mean (SD) response in VWM was significantly shorter ($p=0.015$) than in VWOM groups. This led to a significantly shorter hospital stay period in the VWM group compared to VWOM group ($p=0.003$).

Table 2. Mean (SD) total vancomycin doses; response and hospital stay period and frequency and percent of gram positive infection in the VWOM and VWM groups

	VWOM	VWM
Total vancomycin doses (mg/kg)	608 (201)	606 (279)
Frequency and percent of gram positive infection	32 patients (64%)	31 patients (62%)
Response (Days)	8.7 (3.6)	6.5 (2.5)
Hospital stay period (Days)	12.4 (4.2)	10.1 (3.4)

Figure 1 shows the results of the therapeutic drug monitoring of vancomycin in VWM group.

Table 3 shows the mean (SD) total vancomycin doses in mg/kg of sub-therapeutic and toxic patients within the VWM group when monitored and if was not monitored.

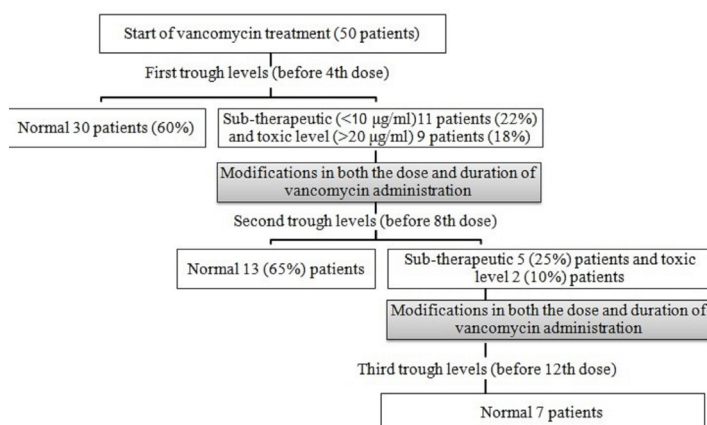


Figure 1. Results of the therapeutic drug monitoring of vancomycin in VWM group

Table 3. Mean (SD) total vancomycin doses in mg/kg of sub-therapeutic and toxic patients in the VWM group when monitored and if was not monitored.

		Actual total dose when monitored (mg/kg)	Total dose if was not monitored (mg/kg)
First trough levels	Toxic (9 patients)	586.7 (261.2)	337.2 (175.9)
	Sub-therapeutic (11 patients)	692.7 (180.7)	887.7 (317.5)
Second trough levels	Toxic (2 patients)	360.0 (0.4)	197.0 (38.9)
	Sub-therapeutic (5 patients)	624.0 (172.9)	830.0 (415.6)

Discussion

Monitoring vancomycin serum trough level is recommended for patients with unstable renal function [19]; those receiving prolonged courses of therapy (more than three to five days) [9] and oncology patients [19, 20].

Similar to previous literatures, [6-8] the introduction of vancomycin in the treatment with other nephrotoxic agents (VWOM) showed higher number of patients with nephrotoxicity compared to vancomycin free group (VF). On the other hand, vancomycin monitoring decreased the nephrotoxicity in VWM group compared to VWOM group ($p=0.016$) and reached a similar result of VF group [6,19,21]. This findings support the idea of monitoring vancomycin when added to the treatment of pediatric cancer patients.

The previous similar studies results were associated with shorter courses of therapy, less total doses of vancomycin and hospital stay [6,19,21]. In our work, there was a significant improvement in response achievement ($p=0.015$) in monitored group compared to non-monitored group. This led to a significantly shorter hospital stay period in the monitoring group ($p=0.003$). However, there was no significant difference between the total vancomycin dose delivered to the VWM and VWOM groups. This could be attributed to the presence of high number of patients with sub-therapeutic trough levels in the VWM group who needed to increase their dose. This high number of patients with sub-therapeutic trough levels could be explained by the incompletely understood increase in metabolism and elimination of the vancomycin in children with cancer, which might results in reduction in its serum concentrations [22,23]. However, we should state that monitoring corrected therapy in both types of patients. It fixed the possible failure of therapy in sub-therapeutic patients and decreased the possibility of toxicity in toxic group of patients. Hence, we can say that there was a lower total dose administrated of vancomycin in patients with toxic trough levels as shown it Table 3.

It was previously shown that monitoring improved the clinical outcomes, adverse effects and reduced the incidence of nephrotoxicity in patients with hematologic malignancies [24]. Also, it was previously demonstrated that monitoring improved cost-effectiveness in ICUs patients [19,25], those receiving other nephrotoxins and oncology patients [19,20].

Many experts do not recommend measurement of serum vancomycin concentrations in patients with normal renal function who are treated with the usual dosages of vancomycin [12,20,26,27]. However, the work presented here advice against this recommendation in pediatric cancer patients with normal renal function when vancomycin is added to their treatment which mostly contains different types of nephrotoxic agents.

Conclusions

Vancomycin serum level monitoring in the studied type of patients led to a decrease in nephrotoxicity, duration of vancomycin administration and hospital stay. Although there was no significant difference in total vancomycin doses between monitored and unmonitored groups; dose modification of monitored patients was effective in bringing safe and effective vancomycin dose to the toxic and sub-therapeutic patients. Consequently, the vancomycin serum level monitoring is of importance in the high risk groups studied of pediatric cancer patients treated with different nephrotoxic agents. We recommend to monitor this risk group when using vancomycin for long term.

Author Disclosure Statement.

No competing financial interests exist.

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