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Original article

High sensitivity versus low level of vancomycin needs to be concern for another alternative anti- *Staphylococcus aureus* as the first- line antibiotic

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Summary. *Background and aim:* Vancomycin has been the first-line therapy for MRSA infection disease for many years. According to standard guidelines, the therapeutic vancomycin trough concentration should be above 10 mg/L and optimally between 15-20 mg/L. The aim of this study was to evaluate vancomycin trough level concentration in patients infected with MRSA. *Methods:* This cross- sectional study included a sample of 170 patients admitted to the ICU of Loghman hospital. We used a standard questionnaire, then applied appropriate statistical tests. All collected data had been analyzed and interpreted by IBM SPSS Statistics 19.0. *Results:* Among this study population, 71.8% was male. Just 20.8% of the patients can reach the therapeutic level trough even after changing the dose. It should be noted that a significant percentage of toxicity was observed after increasing the dose. *Conclusions:* Even though high sensitivity against vancomycin disc has been seen in antibiogram tests, sufficient efficiency has not been distinguished, in the sense that, just a few patients by low trough level concentration, reached to therapeutic level after the dose change. Based on some sources, because of the side effects and limited safe range of vancomycin, we should consider a new approach to the alternative antibiotics. (www.actabiomedica.it)

Key words: vancomycin, trough level, MRSA, toxicological intensive care unit

Introduction

Vancomycin is a glycopeptide antibiotic which has been used since the 1950s against gram-positive bacteria especially MRSA (methicillin-resistant *Staphylococcus aureus*) (1, 2). MRSA can cause different infectious diseases such as sepsis, endocarditis, osteomyelitis, infection of tissues, skin, and different kinds of pneumonia including aspiration pneumonia and Ventilator associated pneumonia (VAP) (3, 4). Nowadays, vancomycin is the first-line therapy and gold-standard treatment for MRSA infection disease (5-7). Vancomycin level trough has a limited range. In order to achieve appropriate and safe clinical response, IDSA (Infectious Diseases Society of America)/ASHP (American Society of Health System Pharmacists') have published guidelines in 2009(8). According to these, the therapeutic vancomycin trough concentration should be above 10 mg/L and optimally between 15-20 mg/L. Furthermore, vancomycin associated nephrotoxicity usually happens when the measured concentration of the drug is higher than 20 mg/L (9-11). The relationship between trough level and efficacy of vancomycin, or microorganism eradication is not supported by clin-

ical data, but for adverse effects prevention, trough level monitoring is necessary. There is a especial concern about the adverse effects of vancomycin treatment for infected patients. The red man syndrome and nephrotoxicity are the most important problems, which can be caused by this broad spectrum antibiotic (12, 13). While vancomycin associated nephrotoxicity is usually reversible, it may increase the medical costs, the average length of stay in hospitals, and in rare cases lead to dialysis treatment and finally death. Vancomycin dose, duration of treatment, and personality characteristics of patients are the most important factors for nephrotoxicity (14-16). For these reasons, vancomycin is one of the most-studied antibiotics in the world (17, 18). The prediction and prevention of drug toxicity according to serum level concentration is the controversial issue. This process is time-consuming and costly because of sample collection and data analysis, write order, and interpretation of results. Dramatically, due to last year`s reports in Loghman hospital, the most evaluated vancomycin trough level has shown a range between 4.5-7 mg/L, which is not acceptable according to scientific guidelines. The aim of this study was to evaluate vancomycin trough level concentration in patients infected with MRSA.

Methods

This cross-sectional study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Research project number 47.2018.3.11). The study included a sample of 70 patients admitted in the ICU department of Loghman hospital as well as 100 medical records of patients who were admitted and discharged during 3 years from Jun 2015 to March 2017. All poisoned patients with infection who were referred to the ICU were included in the study. Nephrotoxic patients and those who had cancer as well as patients who used another antibiotic instead of vancomycin were excluded. Among all the patients, 122 (71.8%) were male. We used a standard questionnaire including clinical, demographic data and Lab tests sections. Patient data including age, gender, vancomycin doses, hospital length of stay, vancomycin treatment length, the type of toxicity, vancomycin trough level concentration, serum creatinine, and culture results (blood, tracheal, and urine culture) were collected from their medical records. The type of microorganisms causing infection were classified as *staphylococcus*, *streptococcus*, *gram-negative bacilli*, and fungus. In addition, the antibiogram test results were recorded for 121 infected patients, and the sensitivity against vancomycin was detected. Aspiration pneumonia, ventilator-associated pneumonia, and sepsis as *staphylococcus aureus* associated infections were considered. In order to evaluate vancomycin effectiveness, the vital signs consisting of body temperature; pulse rate, respiratory rate, Glasgow Coma Scale (GCS), blood pressure; and laboratory tests including urea, creatinine, WBC, Na, K, creatinine phosphokinase (CPK) were recorded the day before treatment and 3 days after treatment. Rhabdomyolysis was defined as the CPK above 1000 U/L. The type of toxicity, which is classified as opiate overdose, drug stimulant toxicity, benzodiazepines toxicity, and mixed drug toxicity, were precisely documented. ECL (electrochemiluminescence) measured evaluable trough concentrations. If the trough levels were under therapeutic range, we measured these for a second time after dose changing. Although the AUC/MIC ratio is the best predictor of vancomycin efficacy, we could not afford it financially. Appropriate statistical tests such as paired T-test, chi-square, Wilcoxon signed-rank test, and exact Fisher tests were applied. All collected data were analyzed and interpreted by IBM SPSS Statistics 19.0.

Results

Among this study population, 71.8% was male. The mean hospital duration was 19.12 days (median=14.5). The most common poisoning was opioid overdose (30%). The next important agents have been shown in Table 1. Only 13 patients had an underlying disease such as depression, hypothyroidism, and brain tumor. Defining leukocytosis as WBC count ≥10000, pre- treatment 51.8% had leukocytosis, while this figure dropped to 41.8%, 3 days after treatment (p value=0.03). In the other hand, leukopenia which indicates severe infection, was observed in just five patients at first and then in one person after 3 days (Table 3).

Pulmonary involvement was detected in 96.5% of the study population in the forms of aspiration pneumonia (AP) (53.5%), VAP (74.1%); some of them were both dependent on the onset. In 29.7% of patients, rhabdomyolysis had occurred. The mean body temperature on the day before treatment was 38.02 c (36c - 40.3c), and 37.6^{0}c at 3 days after treatment (36c - 40c), which indicates a significant change (p value=0.0001). According to some standard definitions, when the second measurement shows the figure 0.3 times rather than the first measurement, creatinine rising was occurring. According to this, 48 people (28.2%) had creatinine rising. Serum creatinine levels were measured 3 times. The initial average was 1.18 (0.5 -9.5), subsequent average was 1.24 (0.5-11.3) and the third, post-dose change average was1.23 Showing no significant differences between creatinine levels. Generally, 96 (59.4%) patients were *Staphylococcus aureus* positive in tracheal, urine and blood culture. Among 170 patients, approximately 90% had positive tracheal culture consist of 45.3% *Staphylococcus aureus*, 34.1% *gram- negative bacilli*, 10% *streptococcus*, 1.2% fungus and 9.4% had negative culture. From 18.9% people with positive blood culture, 11.2% had *Staphylococcus aureus*, 7.1% had gram-negative *bacilli*, 0.6% had *streptococcus*. Urine culture was positive in 26.5% patients. This figure is consisted of 21.2% *gram- negative bacilli*, 2.9% *Staphylococcus aureus*, 1.2% *streptococcus* and 1.2% fungus. The most common dose of vancomycin prescribed was 1 gr.bd (81.7%). Totally, 48 patients with low trough level concentration were required to change the dose of vancomycin. The average duration of drug consumption was 6.3 days (3-90 days, SD=3.3). The most commonly measured first trough level concentration was 13.8 (0.01-55.4, SD=9); concentration, for the second measurement was 16.3 (SD=9) (Table 2). The antibiogram test was performed for 91 cases that had positive tracheal culture. These results showed 96.8% sensitivity and 3.2% resistance against vancomycin disc. In the case of urine culture, these percentages were reported to be 71.4% sensitive, 14.3% intermediate and 14.3% resistant. The sensitivity reporting for

Table 1. Patient characteristics

Gender	Number/percent
Male	122 (71.8%)
Female	48 (28.2%)
Kind of drug toxicity	Opioids 51 (30%)
	BZD 30 (17.6%)
	Stimulants drugs 7 (4.1%)
	Opioids and BZD 37 (21.8%)
	Other agents** 25 (14.7%)
	MDT * 8 (4.7%)
	Opioids and stimulants drugs 12 (7.1%)
Average hospital duration	19.12
Vancomycin sensitivity (Tracheal Culture) (Disc diffusion method)	Sensitive 91 (96.8%)
	Resistant 3 (3.2%)
Vancomycin sensitivity (Blood Culture)	Sensitive 20 (100%)
Vancomycin sensitivity (Urine Culture)	Sensitive 5 (71.4%)
	Intermediate 1 (14.3%)
	Resistant 1 (14.3%)

* Multi drug toxicity such as the mixture of sodium valproate, acetaminophen, Benzodiazepines, …
** Others agent included: Aluminium phosphide, Tricyclic antidepressants (TCAs), Carbon monoxide (CO), Acetaminophen

Table 2. Patient's vancomycin serum level concentration

Trough level concentration	<10 mg/l	10-15mg/l	15-20 mg/l	>20 mg/l	Total
First measurement	70 (41.17%)	45 (26.4%)	27 (15.8%)	28 (16.4%)	170
Second measurement	12 (25%)	12 (25%)	10 (20.8%)	14 (29.2%)	48

Table 3. Comparison of Leukocytosis, Leukopenia and fever, before and after the treatment

	Before treatment	3 days after treatment	p value
Leukocytosis	88 (51.8%)	71 (41.8%)	0.03
Leukopenia	5 (2.9%)	1 (0.5%)	
Fever	138 (81.2%)	100 (58.8%)	0.0001

blood culture was 100%. The relationship between sex ratio and trough level concentration is not significant (p value=0.2). Based on body temperature ≥37.5c defined as fever, before and after treatment, 81.2% and 58.8% of cases had fever, respectively (p value=0.0001).

Discussion

As the incidence of MRSA infection rises, the prescription of vancomycin as the first line therapy has increased. Vancomycin still is one of the most studied antibiotics in the world because of its limited safe range and side effects (5-7, 19-22). According to published data, there is a strong relationship between high doses vancomycin therapy and nephrotoxicity. However, studies have suggested that nephrotoxicity usually occurred at vancomycin levels above 20 mg/dl, thus the target dose suggesting by standard guidelines 15-20 mg/dl may increase the risk of nephrotoxicity. Additional factors may include co-ingestion of nephrotoxic agents, duration of therapy, and underlying physiological impairment (15, 19, 23, 24). We did not detect the expected any significant differences in the serum creatinine levels (p value=0.4). We realized that rhabdomyolysis may cause initial creatinine rise. The specific conditions of our patients may justify this position, most poisoned with nephrotoxic substances as confounding factors. Although it has been claimed that vancomycin-associated nephrotoxicity is usually reversible, our previous studies showed in some cases with rhabdomyolysis, the nephrotoxicity was irreversible (25). Ultimately, this is a controversial issue because of the differing definitions of nephrotoxicity. Some studies such as Lodise et al. have indicated the association between other drugs such as aminoglycosides and amphotericin B with nephrotoxicity (26). In our study, we tried to exclude the patients who used other antibiotics or nephrotoxic drugs.

According to Talaie et al. a significant number of patients in the poison center, who were infected by MRSA, could not reach an appropriate trough level after vancomycin therapy. Their results have shown the most of the patients had a trough level between 4.5-7 mg/l, which is not an acceptable level. This pilot study prompted them to carry out additional research and design this study (25).

The prevalence of *staphylococcus aureus* is 59.4% of all microorganisms in blood, tracheal and urine culture. This is the most common germ in our study. Even though in antibiogram test, the high sensitivity against vancomycin disc has been seen, sufficient efficiency has not been distinguished. In the sense that, just a few patients with initial low trough level, reached the therapeutic level after the dose change. As a study shown that the length of hospital stay (LOS) had a significant effect on vancomycin side effects, we should mention that LOS was an appropriate indicator of morbidity and mortality(27).

Eun Young Choi's study found that in patients infected with MRSA nosocomial pneumonia, the rate of relapse was high and the clinical outcome was not effective enough when treated with vancomycin (28). Some suggest that given the high cost and long term consumption required by vancomycin, as well as its side effects and limited safe range, we should consider a new approach to the alternative antibiotics (29, 30). In addition, the use of an alternative medicine to vancomycin, may not require such monitoring (9).As in recent years , the dominant microorganisms of the toxicological ICU, have been and still are *staphylococcus aureus*, the need for an effective antibiotic as an alternative to vancomycin is felt.

The most important issue to be noted in the present study is that, after changing dose in order to achieve optimum outcomes, not only did the toxic level occur, but also in some cases, the therapeutic level was not obtained. It is necessary to mention that some complications such as red man syndrome, leukopenia and pancytopenia, as vancomycin side effects, were not reported in this study.

We had several limitations in this present study; first, the study population was relatively small. It would be better to enroll more people in order to increase the study power. Second, we lost some of the cases during the study because of high turnover in our ward or expiry. Third, some of the patients have other multidrug-resistant pathogens as a confounding factor, for example, carbapenem-resistant Acinetobacter and extended-spectrum beta lactamase-positive Gram-negative organisms, although these were treated well. And finally one of the limitations of our study was that the E-test was not available for a long time due to economic sanctions.

Finally, the logical conclusion from this study is that alternative anti- staph broad-spectrum antibiotics are immediately necessary.

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