Common Errors Related to Vancomycin Pharmacokinetics, Prescribed by Physicians in Iran: Suggesting Practical Approaches for Adjusting the Right Dose

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ABSTRACT

Background: Vancomycin is a glycopeptide antibiotic that is widely used for the treatment of gram-positive microorganisms, including methicillin-resistant Staphylococcus aureus. It is a valuable antibiotic in practice; unfortunately, its excessive use and mistakes in prescription have increased bacterial resistance. Hence, this study seeks to investigate the common errors related to the pharmacokinetics of vancomycin prescription in teaching hospitals in Iran.

Methods: This study is an observational study that research orders with errors related to pharmacokinetics parameters of vancomycin. A total of 150 patients were enrolled in the study from May 2016 to September 2018 in teaching hospitals. Errors in drug prescription were identified based on literature resources.

Results: About 22.7% of patients did not receive the loading dose. Also, 85.3% of patients were prescribed a fixed dose, instead of weight-based dosing. About 46% of patients had kidney problems (chronic kidney disease or acute kidney injury) and all of them had received a much lower dose than they needed according to guidelines. Another 46% of patients did not undergo therapeutic dose monitoring correctly. Finally, 69.3% of patients had not received consequent doses after encountering a nontherapeutic trough level correctly. Also, none of 22 obese patients with a body mass index of greater than 40 kg/m², had received the proper dose.

Conclusion: Since the incorrect use of vancomycin significantly increases the prevalence of resistant organisms and, consequently, the mortality rate of patients, it is necessary to define guidelines for its use in the hospital.

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1. Introduction

Vancomycin is a glycopeptide antibiotic that has been in clinical use for a long time to treat the strains of Staphylococcus aureus [1, 2]. It is one of the most widely used antibiotics for the treatment of serious gram-positive infections, including Methicillin-Resistant S. Aureus (MRSA) [2], which is the most prevalent multi-drug resistant gram-positive pathogen in the world [2]. Unfortunately, excessive use of vancomycin during recent years has resulted in the development of vancomycin resistance strains, including vancomycin-resistant enterococci worldwide [3].

Errors related to medication prescription and administration are the most common type of medical errors in primary and secondary healthcare centers [4]. Kuo et al. reported that prescription errors account for 70% of medication errors, which increase morbidity and mortality for the patients [4]. In a study in Iran, more than half of the patients (56.2%) received vancomycin inappropriately, and the correct indication of prescribing was from 32% at the beginning of the prescribed period to 30.5% after 24 hours and 9% after 72 hours, and only 5.5% of the patients received the medication reasonably [5].

All types of vancomycin medical errors may happen during the prescription and administration phase, like administering the wrong drug for a specific indication, neglecting drug interactions or intravenous incompatibilities, prescribing the wrong dose. These mistakes concerning the pharmacokinetic profile of vancomycin may lead to a nontherapeutic serum trough level despite choosing the proper antibiotic, which consequently results in vancomycin resistance or toxicity.

Regarding the concerns in this issue, and the lack of appropriate alternatives to vancomycin, the rational use of this drug is an important consideration. It seems necessary to prevent prescribing errors of vancomycin, which may lead to vancomycin resistance due to a nontherapeutic trough level and an increase in mortality rates of the patients. We tried to investigate common pharmacokinetics mistakes in the administration of vancomycin in Iran and provide rational guidelines for the appropriate dosing based on pharmacokinetic parameters.

2. Methods

This research was conducted at five teaching referral hospitals in different fields such as “Infectious diseases”, “Nephrology Diseases”, “Cardiac surgery”, “pulmonary diseases”, and “Gastrointestinal diseases” in Tehran. An observational study was done from May 2016 to September 2018. We reviewed all orders of vancomycin in the wards of the hospitals, including the intensive care units. Indications for ordering vancomycin were considered in each ward, and the prescribed dose, along with other aspects of vancomycin, were evaluated based on pharmacokinetic parameters. Any inpatient older than 12 years was included in the study.

A total of 150 patients and their vancomycin orders were evaluated during our rotations in 5 hospitals. These patients were admitted to the hospital at the time we spend there, and all of them were evaluated. The six mostly done mistakes related to pharmacokinetic parameters were sought: neglecting the loading dose, prescribing a fixed dose regardless of patient weight, extreme dose adjustment in renal failure, lack of therapeutic dose monitoring or not doing it properly, wrong approach to a nontherapeutic trough level, and inappropriate dose of vancomycin in obese patients or patients with volume status changes. The study data were gathered and entered into SPSS V. 23, and the frequency and percentages of each error were calculated.

3. Results

Results are shown in Table 1. Note that some patients had more than one prescribing error. Among 150 patients, the loading dose was neglected in 34 patients (22.7%). A fixed dose (instead of weight-based dosing) was prescribed for 128 patients (85.3%). The area under the serum concentration time curve (AUC) / Minimum Inhibitory Concentration (MIC) ratio was calculated for the patients based on the formula presented in “Clinical Pharmacokinetics” (explained thoroughly in the discussion section) [6]. Among 128 patients who had received a fixed dose regardless of their weight, 79 patients (61.7%) achieved the AUC/MIC ≥400, and the others did not meet the goal. Among the other 22 patients who had received weight-based dosing, 19 patients (86.4%) achieved the AUC/MIC ≥ 400 (P=0.02).

Out of the study patients, 69 (46%) had kidney problems (chronic kidney disease or acute kidney injury), and all of them had received a much lower dose than they needed according to guidelines [7]. Also, 69 patients (46%) did not undergo therapeutic dose monitoring cor-
Another 104 patients (69.3%) had not received consequent doses after encountering a nontherapeutic trough level correctly. Finally, none of 22 patients with a Body Mass Index (BMI) of greater than 40 kg/m² had received the proper dose.

4. Discussion

Neglecting the loading dose

Out of 150 patients, 34 patients (22.7%) had not received the loading dose of vancomycin. For the treatment of severe MRSA infections, such as endocarditis, pneumonia, meningoitis, and sepsis, a loading dose of 25-30 mg/kg is recommended (based on actual body weight) to reach the desired trough concentration during the first 24-48 hours [8-10]. Given the risk of red man syndrome and possible anaphylaxis associated with large doses of vancomycin, the infusion time must be prolonged [11]. Each 1 g of vancomycin must be administered at least in 1 hour [8, 12]. A maximum single dose should not exceed 2000 mg [8] or 2500 mg [9]. Stanford university medical center suggests dose adjustments of 15-20 mg/kg² to be considered in patients with pre-existing renal failure [8].

Loading dose was neglected in 22.7% of hospitalized patients with serious infections. Because of the importance of achieving the therapeutic level soon for eradicating dangerous, life-threatening pathogens, it is necessary to consider a loading dose [9].

Prescribing a fixed dose instead of weight-based dosing

A fixed dose (instead of weight-based dosing) was prescribed for 128 patients (85.3%). The administration of vancomycin should be based on the weight of each patient. The parameter that best predicts the efficacy of vancomycin is the ratio of AUC to MIC [13]. The susceptibility breakpoint of vancomycin is 2 mg/L for S. aureus, and 4 mg/L for coagulase-negative Staphylococcus and Enterococcus spp, set by the Clinical and Laboratory Standards Institute (CLSI) [14], meaning that all S. aureus isolates with MICs of 2 mg/L or less and all coagulase-negative Staphylococcus and Enterococcus spp with MICs of 4 mg/L or less are susceptible to vancomycin, and the higher MICs are intermediate or resistant [14].

Despite these breakpoints, some reports have suggested that patients infected with S. aureus isolates who have MICs of 1-2 mg/L are less likely to have treatment success with vancomycin compared with those with lower MICs [13]. The AUC/MIC ratio of ≥400 is reasonable for pathogens with a MIC of 1 mg/L [13]. With higher MIC, the AUC must be higher to achieve treatment success [13]. In general practice, the MIC is considered to be 1 mg/L while using vancomycin as an efficient option [15-17]. A study involving patients with lower respiratory tract infections caused by S. aureus reported that an AUC/MIC ≥400 compared with an AUC/MIC<400 was associated with improved clinical response and microbiologic eradication [18]. Here are some practical formulas derived from the book “Clinical Pharmacokinetics” for calculating vancomycin dosing based on the AUC/MIC ratio to understand its importance [6].

Estimating initial dose of vancomycin:

Step 1: Consider the loading dose of 25-30 mg/kg²

Step 2: Maintenance dose should be based on 15-20 mg/kg every 8-12 hours

Step 3: Calculate vancomycin clearance (Clvanc). Clearance of vancomycin is achievable through various

<table>
<thead>
<tr>
<th>Error Type</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neglecting the loading dose</td>
<td>34 (22.7)</td>
</tr>
<tr>
<td>Prescribing a fixed dose instead of weight-based dosing</td>
<td>128 (85.3)</td>
</tr>
<tr>
<td>Extreme dose adjustment in renal failure or intermittent hemodialysis state</td>
<td>69 (46)</td>
</tr>
<tr>
<td>Lack of therapeutic dose monitoring or doing it not properly</td>
<td>69 (46)</td>
</tr>
<tr>
<td>Wrong approach to a nontherapeutic trough level</td>
<td>104 (69.3)</td>
</tr>
<tr>
<td>Inappropriate dosing of vancomycin in obese patients and patients with volume status changes</td>
<td>22 (14.7)</td>
</tr>
</tbody>
</table>
formulas, according to previous studies, the Matzke et al. [19] formula is closer to actual results (Formula 1) [6]. For example, for an individual with Glomerular Filtration Rate (GFR) = 120 mL/min:

Formula 1.

\[
Clvanc \text{ (mL/min)} = (0.689 \times \text{ creatinine clearance (CrCl)}) + 3.66 \text{ (Matzke method)}
\]

\[
Clvanc \text{ (mL/min)} = (0.689 \times 120) + 3.66
\]

\[
Clvanc \text{ (mL/min)} = 86.34 \text{ mil/min}
\]

\[
Clvanc \text{ (L/h)} = 86.34 \text{ mil/min} \times 0.06 = 5.180 \text{ L/h}
\]

Step 5: Calculate AUC\text{0-24h} Using Formula 2:

Formula 2.

\[
AUC\text{0-24h} = \frac{\text{Daily dose}}{\text{Vancomycin clearance}}
\]

In a person with a dose of 500 mg BD (twice a day):

\[
AUC\text{0-24h} = \frac{1000}{5.180} = 193
\]

In a person with a dose of 750 mg BD: AUC\text{0-24h} = \frac{1500}{5.180} = 289

In a person with a dose of 1 mg BD: AUC\text{0-24h} = \frac{2000}{5.180} = 386

In a person with a dose of 1250 mg BD: AUC\text{0-24h} = \frac{2500}{5.180} = 482

Assuming the 1250 mg BD dosing:

If MIC was 0.5 mg/L: AUC24/MIC = 482 mg•h/L/0.5 mg/L = 964

If MIC was 1.0 mg/L: AUC24/MIC = 482 mg•h/L/1.0 mg/L = 482

If MIC was 2.0 mg/L: AUC24/MIC = 482 mg•h/L/2.0 mg/L = 241

In general practice, MIC is considered to be 1 mg/L. Regarding the difficulties in calculating AUC in clinical practice, measuring serum trough levels of vancomycin (minimum concentration of vancomycin can be measured just before the next dose in the steady-state level) is a practical alternative that correlates with AUC. For the treatment of the infection related to the endocardium and bacteremia, the trough concentrations of 15-20 mg/L is ideal [13].

Trough concentrations less than 10 mg/L are associated with an increase in the development of vancomycin resistance [20, 21]. In these patients, 1250 mg twice a day is expected to produce a 15-20 mg/L trough level as it produces an AUC/MIC ratio of 486, which is higher than 400 and correlates with trough level of greater than 15 mg/L [22, 23]. In an individual with a body-weight of 85 kg and normal kidney function, the dose of 1 g BD (twice a day) will not achieve the AUC/MIC ≥ 400. In cases with MIC >1 mg/L, the AUC/MIC ratio above 600-700 will be the goal of treatment that will increase the risk of renal toxicity [24].

The probability of achieving target AUC/MIC >400 is 100% for vancomycin MIC of 0.5 mg/L and 0% of the MIC value of 2 mg/L even if aggressive dosing strategies are used [25]. In patients with normal renal function, up to 3-4 g/d of vancomycin may be required to attain the target AUC/MIC ratio.

Vancomycin is injected at a dose of 15-20 mg/kg every 8 to 12 hours. If the MIC is 1 mg/L or less, the dose of 1 g BD could produce an AUC/MIC ratio of >400 in a proportion of subjects, not all of them. The data from animal models, in vitro and human studies, suggest that microbiologic success is optimized when the vancomycin AUC/MIC ratio exceeds 400. Also, to improve the clinical outcomes of complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by S. aureus, total trough serum vancomycin concentrations of 15–20 mg/L are recommended to achieve target AUC/MIC [11, 13, 18, 26, 27].

Our recommendations are in line with a study done by Shahrami et al. that the necessity of early individualization and weight-based dosing of vancomycin was required for achieving goal trough levels, and the fact was concluded based on the results [28].

**Extreme dose adjustment in renal failure or intermittent hemodialysis state**

All of the patients with kidney problems had been received much lower doses than they should. Most physicians reduce vancomycin dosing, more than it is needed, in renal failure or patients on intermittent hemodialysis with concerns about nephrotoxicity. This action results in subtherapeutic concentrations of vancomycin and increasing the risk of treatment failure. Dose adjustment in renal failure should be made as follows in Table 2 [7].
Intermittent hemodialysis

Loading dose must be considered (15-20 mg/kg), regardless of the dialysis schedule and patient renal function; this ensures rapid target concentration attainment. A random level should be drawn before the next hemodialysis session, and the trough level measured should guide the post hemodialysis dosing, as 30%-40% of vancomycin is removed after each high-flux hemodialysis session [29]. Patients should receive the drug again (usually 15 mg/kg) when the random vancomycin concentrations are less than 10-20 mg/L depending on the severity of the infection.

Random vancomycin concentrations of 15-20 mg/L are recommended for severe infections [29]. In a study, a loading dose of 1000 mg was considered during dialysis and subsequent 1-g doses were administered at the last hour of each dialysis session and almost the whole patients achieved serum trough level of more than 10 mg/L before the fourth dose and only 5% had a serum trough level of greater than 25 mg/L [30]. Physicians mostly neglect the two consecutive days and administer every 48-72 hours from the first day of therapy.

Continuous renal replacement therapy

Proper dosing of vancomycin in continuous renal replacement therapy requires close monitoring of therapeutic response, signs of adverse reactions due to drug accumulation, and target trough concentrations. The dosing recommendations are as follows [31]:

- Continuous venovenous hemofiltration: A loading dose of 15–25 mg/kg, followed by 15 mg/kg every 24–48 hours or 500 mg q 24 h to 1500 mg q 48 h.
- Continuous venovenous hemodialysis: A loading dose of 15-25 mg/kg, 15 mg/kg every 24 h or 1-1.5 g q 24 h.
- Continuous venovenous hemodiafiltration: A loading dose of 15-25 mg/kg, 15 mg/kg every 12 h or 1-1.5 g q 24 h.

Dose adjustment in acute kidney injury

Adjusting Vancomycin dosing is not always necessary in AKI secondary to sepsis, as a rise in serum creatinine is a predictor of achieving a trough level of more than 15 mg/L [32]. Regarding the action of therapeutic dose monitoring, dose adjustment can be done whether supra/sup therapeutic concentrations of vancomycin are detected. Table 3 shows the diagnostic criteria of AKI based on AKIN and RIFLE criteria [33].

Lack of therapeutic dose monitoring or doing it improperly

A total of 69 patients (46%) did not undergo therapeutic dose monitoring correctly in our study. Measuring the vancomycin trough level is not always required. In patients with stable renal function, which the duration of treatment with vancomycin is expected to be ≥3-5 days, no therapeutic dose monitoring is needed [13]. Otherwise, trough concentrations of vancomycin are required as a marker to predict the AUC/MIC ratio. Vancomycin trough concentrations of 10-15 mg/L may be

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**Table 2. Vancomycin dosing guide in renal failure**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40-55</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>500 mg</td>
<td>Q8H</td>
</tr>
<tr>
<td>750 mg</td>
<td>Q12H</td>
</tr>
<tr>
<td>1000 mg</td>
<td>Q24H</td>
</tr>
<tr>
<td>16-20</td>
<td>Q48H</td>
</tr>
<tr>
<td>13-15</td>
<td>Q60H</td>
</tr>
<tr>
<td>10-12</td>
<td>Q72H</td>
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</tbody>
</table>

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acceptable in the skin and soft tissue infections. A minimum trough concentration of 10 mg/L is required to avoid resistance development [20]. However, a trough concentration of at least 15 mg/L is required for more severe infections [34].

For patients with an estimated creatinine clearance (CrCl) of ≥20 mL/min, vancomycin trough levels should be drawn before the fourth dose (steady state). Measuring trough concentrations before steady-state concentration may overestimate or underestimate the exact concentration. For patients with an estimated CrCl <20 mL/min, a random level can be drawn on day 3 (24 hours after the second dose) [13].

Follow-up trough concentrations can be performed weekly in hemodynamically stable patients. More frequent vancomycin trough concentrations may be required in critically-ill patients, individuals with unstable renal function or on concomitant nephrotoxic drug therapy, older patients with every 8 hours dosing administration, and patients who do not respond or deteriorate on current dosing. Note that the vancomycin trough level should not be drawn from the same infusion site [35].

The wrong approach to a nontherapeutic trough level

About 69.3% of patients did not receive the proper dose or interval after developing a nontherapeutic trough level. Based on our observations, clinicians generally increase the dosage in the case of nontherapeutic trough level or hold and reduce the dose if the trough is above the therapeutic limit, which is not necessarily correct. A practical approach when encountering a nontherapeutic trough level is as follows [36]:

\[
\text{new} = \left( \frac{\text{new}}{\text{current}} \right) \times \left( \frac{\text{desired}}{\text{measured}} \right)
\]

If the ratio of C desired/C measured is 1.5 or higher, the interval should be reduced (from 8 hours to 12 hours, from 12 hours to 24 hours or from 24 hours to 36 hours). If the ratio is between 0.67 and 1.5, then the dose will be altered without changing the interval.

For example, in a person with pneumonia who is on vancomycin 750 mg BD with a trough level of 10 mg/L, the desired trough is 15-20 mg/L. The ratio of the desired trough (17 mg/L) to the measured (10 mg/L) one is 1.7 which is higher than 1.5. So intervals should be reduced to every 8 hours without changing the dose.

If the trough level measured was 13 mg/L, the ratio (1.30) is between 1.5 and 0.67. So the dose should be altered without changing the interval:

\[
\text{new} = \frac{\text{new}}{\text{current}} \times \frac{\text{desired}}{\text{measured}}
\]

\[
\text{new} = 13 \times \frac{17}{10} = 22.1 \text{ mg/L}
\]

Note that “c” refers to the concentration of vancomycin in human serum.

For example, in a person with pneumonia who is on vancomycin 750 mg BD and trough level of 13 mg/L, the desired trough is 15-20 mg/L.

\[
\text{new} = 750 \times \frac{17}{13} = 980 \text{ mg BD}
\]

Another simple equation for calculating the new dose in situations which the ratio of C desired/C measured is between 1.5 and 0.67 is as follows: Dose new =Dose current \times \left( \frac{\text{desired}}{\text{measured}} \right).

GFR: Glomerular Filtration Rate; RRT: Renal Replacement Therapy

Table 3. Diagnostic criteria of acute kidney injury based on AKIN and RIFLE criteria

<table>
<thead>
<tr>
<th>Stage (Severity)</th>
<th>Serum Creatinine Concentration</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (risk)</td>
<td>1.5–2x increase from baseline; or ≥0.3 mg/dL; or decrease in GFR &gt;25%</td>
<td>&lt; 0.5 mL/kg/h for &gt;6 h</td>
</tr>
<tr>
<td>Stage 2 (injury)</td>
<td>2–3x increase from baseline; or decrease in GFR &gt;50%</td>
<td>&lt; 0.5 mL/kg/h for &gt;12 h</td>
</tr>
<tr>
<td>Stage 3 (failure)</td>
<td>3x increase from baseline; or &gt;4 mg/dL with an acute rise &gt;0.5 mg/dL; or on RRT; or decrease in GFR &gt;75%</td>
<td>&lt; 0.3 mL/kg/h for 24 h, or anuria for &gt;12 h</td>
</tr>
</tbody>
</table>

Generally, in low trough concentration, the dose of 750 mg BD will be increased to 1000 mg BD by physicians, which is not necessarily a correct approach, because it may still cause treatment failure.

Estimating the new AUC from the new dose is also possible from this simple equation:

\[ AUC_{new} = AUC_{current} \left( \frac{D_{new}}{D_{current}} \right)^n \]

Trough concentration of vancomycin must be re-evaluated after determining the new dose and interval by the fourth dose or earlier if the patient is hemodynamically unstable with alterations in renal function or if the dosing interval is >24 hours. Note that whenever the trough level is above the goal (20-25 mcg/mL for a target of 15-20 mcg/mL), it is better to continue treatment with the new dose rather than holding vancomycin administration. Trough levels can be measured before the fourth dose after adjusting the new dose.

Inappropriate dosing of vancomycin in obese patients and patients with volume status changes

All of the obese patients in our study (14.7%) received a lower dose than they should. Physicians mostly prescribe the lower doses of vancomycin (<10 mg/L) in obese patients, concerning its nephrotoxicity, whereas it leads to a nontherapeutic trough level. Vancomycin dosing should be based on actual body weight in obese patients (>30% above ideal body weight), following the loading doses [8, 37]. There is a possibility to increase the dose up to 60 mg/kg/d. Single doses should not exceed 2 g. Each 1 g should not be administered in less than an hour [8, 12]. In the case of a nontherapeutic trough level, shortening the interval or continuous infusion is a reasonable approach [35, 37].

5. Conclusion

Despite extensive clinical use of vancomycin in recent years, the optimal dosing strategy for rapid achievement of therapeutic concentrations has remained a challenge for physicians. Intervention strategies should be primarily focused on the education and creation of a safe and cooperative working environment to minimize harm to the patient. Clinical pharmacists have an essential role in setting the appropriate dose which produces desired trough levels, and it is best to consult them for achieving treatment success.


