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Original Article

Vancomycin Drug Levels and Clinical Correlations in Critical Pediatric Patients

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ABSTRACT

Objective: Vancomycin is an antibiotic frequently used in the treatment of resistant gram-positive infections. Although data on its efficacy and safety in pediatric patients are limited, it is widely used in clinical practice. Recommended trough serum levels are 15–20 mg/L, and peak levels are 20–40 mg/L. To reach these targets, it is generally administered at a dose of 40–60 mg/kg/day depending on the infection type. Pediatric Intensive Care Unit (PICU) admissions frequently involve clinical complexity. In this study, we aimed to evaluate the serum levels of vancomycin in patients treated in our unit.

Methods: This retrospective study includes patients who were hospitalized in our PICU between 2015 and 2019, received vancomycin therapy, and had serum vancomycin levels measured.

Results: Data from 14 patients (median age: 45.4 months, 42.9% male) were evaluated. Sepsis (50%) and pneumonia (21.4%) were the leading indications. The median vancomycin dose was 50 mg/kg/day (40–60), with a treatment duration of 7 days (2–10). In total, 30 serum vancomycin levels were analysed. Trough levels were measured in 47.6% and peak levels in 52.4% of patients, respectively. Levels were within the target range in 44.4%, below in 44.4%, and above in 11.1%.

Conclusion: Optimal vancomycin levels in critically ill pediatric patients often necessitate individualized dosing strategies. Close monitoring remains essential to ensure both efficacy and safety.

INTRODUCTION

Vancomycin is a glycopeptide antibiotic that blocks the formation of the bacterial cell wall and is particularly active against resistant gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). It is frequently administered in management of serious gram-positive infections. Its half-life is around 6 hours in patients with normal renal functions, but it can be as long as 7.5 days in anuric cases. After IV administration, 70-90% of the drug is extracted unchanged through glomerular filtration. It cannot be extracted through haemodialysis or peritoneal dialysis.[1]

By therapeutic drug monitoring, it is aimed to keep the blood drug level between therapeutical range, thus having optimal outcome while reducing the risk of drug toxicity. By monitoring the patient during the treatment, it helps us to determine the optimal dosage for the patient regarding their age, weight, renal functions and other variables. Blood drug level monitoring helps us to determine optimal dosage from the drug while having minimal risk of side effects by regarding administration time, desired clinical levels and attainment of a stable state.[1-3]

Sampling time may vary depending on the purpose of the sample, some examples of which may be blood drug levels coherence, toxicity or dose suitability monitorization. Generally, monitorization is based on trough levels instead of peak levels. Trough level is the level right before ad-

ministration of the next those and it shows the lowest concentration of the administered therapeutic dose, while peak level shows the highest concentration after dispersion of the drug after administration. There are many factors affecting peak dose. The route of administration for the drug, formulation of the drug (slow or fast release), additional maladies which may affect gastric motility and pharmacokinetic properties of the drug.[1,4,5]

In routine practice, it is not required to measure serum concentrations for vancomycin. Therapeutic peak level range is 20-40 µg/mL, and trough level range is 5-10 µg/mL. Since irreversible autotoxicity is seen in blood levels above 80 µg/mL, it is more convenient to measure trough levels instead of peak levels. When trough levels are kept in desired range, peak levels cannot be above 40 µg/mL and considering that there is not enough evidence backing peak level toxicity, trough level monitorization is the widely recommended choice. Best time to monitor peak levels is about 1 hour after end of administering IV infusion. Vancomycin trough level monitorization helps dose adjustment in a way that keeps the concentration above minimum inhibitor concentration (MIC) value while preventing accumulation of drug in the body. The most optimal time for trough level measurement is right before administration of third dose. If the trough level is suitable (5-10 µg/mL), renal functions are stable and clinical response is favourable, there is no need for a second trough level measurement. For patients with renal failure, regarding the stage of renal failure, vancomycin through level should be seen 2-5 days after the administered dose, and the next dose should be applied after getting blood concentration in the target range.[1,5-8]

Pediatric Intensive Care Unit (PICU) patients are complicated ones. Managing dosage of antibiotics regarding accompanying organ failures decreases complications, thus reducing mortality and morbidity rates. In our study, we have aimed to examine the serum levels of vancomycin among the patients we have used the drug on.

MATERIALS AND METHODS

This study was conducted following the ethical guidelines outlined in the Helsinki Declaration. Ethical approval was obtained from the Ethical Committee of Marmara University Clinical Research (Date: 12/06/2020, No: 09.2020.649).

In this study, we have retrospectively assessed the files of PICU patients who were treated with vancomycin and had blood level monitorization between 01.01.2015-01.01.2019. Their demographic features, vancomycin treatment dosages and serum drug levels were assessed. Blood samples were obtained from the patients with 2.5 mL tubes (Vacutainer SST II, Becton Dickinson, USA) then centrifuged for 10 minutes at 2500 G at our hospital laboratory. Serum vancomycin levels were assessed by automated device (Cobas Integra 400, Roche Diagnostics, USA) by using fluorescent polarization immunoassay (FPIA) method. As per producer data, coefficient of variation values (CV%) for 8.68-26.3-54.6 mg/L serum vancomycin levels are stated as 2.2%-1.6%-3.1%; and between studies they are shown as 3.0%-2.2%-3.3%. Categorical data is shown as n and % while continuous variables were shown as median (IQR) values.

RESULTS

The data of patients who were treated by vancomycin and had blood level measurement during their stay at our PICU between 2015-2019 were analysed. Of 14 patients with a median age 45.4 (IQR), 42.9% were male (n:6). The most common indication for vancomycin was sepsis (50%) and pneumonia (21.4%). The median duration of vancomycin treatment was 7 days (2-10), and the dose was 50 (40-60) mg/kg/day. During treatment, a total of 30 serum vancomycin levels were sent from 14 patients (once from 6 patients, twice from 4 patients, four times from 2 patients, three times from 1 patient and five times from one patient), and the median level was 18.4 (11.6-31.0, min-max; 5.5-49.0) mg/L. Treatment doses and associated serum vancomycin levels are shown in Table 1. Trough

Table 1. Vancomycin serum concentration levels and administered doses

Vancomycin dose	Serum vancomycin levels (mg/L), Median (IQR)*	
10 mg/kg/day	12.0 (n:1) **	
40 mg/kg/day	15.0 (8.6-29.5) (n:9) **	
60 mg/kg/day	14.6 (9.6-25.8) (n:9) **	
Vancomycin serum readings	First reading	All readings
Median, IR (mg/L)	15.0, 9.1-29.5	18.4, 11.6-31.0
Minimum-maximum	5.5-40.4	5.5-49.0
Trough level		
Median, CAA (mg/L)	10.7, 7.2-35.5	10.9, 7.0-40.0
Minimum-maximum	7.0-40.0	7.0-40.0

Trough level is the level right before the next dose. IQR: Inter quartile range. *p: 0.9, Kruskal Wallis test. **n shows the reading amount, not the patient count.

level was measured in 47.6% of patients and peak level was measured in 52.4% of patients. Serum vancomycin levels were normal in 44.4%, low in 44.4% and high in 11.1%. In 18 patients with normal renal function, vancomycin levels were found to be low in 8(44.4%) patients and normal in 10(55.6%).

DISCUSSION

The studies among adults have shown that increasing MRSA resistance is directly related to the need to increase the vancomycin dose. It has been proven that the clinical effect is correlated with trough levels.[9] Latest pediatric research has shown that the target trough concentration should be 15-20 mg/L and vancomycin overdose is highly correlated with increase in toxicity risk.[10,11] The increase in vancomycin resistance among MRSA has resulted in higher empirical dose usage to reach the target 15-20 mg/L starter trough levels. In pediatric patients, even though the data is limited, the findings are significantly similar. Treatment strategies should be planned in accordance with pediatric data and bacterial resistance tendencies.

Vancomycin is a drug that is known to be nephrotoxic, especially with long term usage. Hidayat et. al. has shown among adults that have MRSA infection who take vancomycin treatment, when they get other nephrotoxic agents with a trough level of 15-20 mg/L, have vancomycin related nephrotoxicity incidence.[12] A study from 2011 has shown adults with MRSA infection have higher renal injury risk with vancomycin trough level ≥15 mg/L (OR, 3.6; 95% CI, 1.75-7.59).[13] Likewise, it was shown in adults with MRSA pneumonia that there is three to five times higher risk of acute kidney injury with a trough level of 15 mg/L or higher.[14,15]

Maloni et al.[16] has shown similar results to our study, as they had reached therapeutic level of 7-14 mg/L at 44.7% of their cases, which is similar to our results of 44.4%. In our unit, we are using vancomycin for treatment of many multidrug-resistant gram-positive infections with a starter dose of 40 mg/kg/day unless there is a suspicion of serious meningitis infection. We are not studying serum levels for every patient who undergoes vancomycin treatment routinely. The serum levels were studied for patients who have partial or no response to therapy, who have organ failure or are at risk of it. The treatment dose is increased up to 60 mg/kg/day if deemed necessary. Due to factors such as the current conditions in the hospital and the availability of test kits, the number of patients studied is not optimal for now.

Conclusion

Our study has importance as a guidance for other studies which contain more patients with additional contributing centres. Critically ill children may require different dosage to reach desired trough concentration for each patient. Vancomycin levels should be monitored closely especially when there is a need to avoid toxicity while reaching treatment serum trough levels.

Ethics Committee Approval

The study was approved by the Ethical Committee of Marmara University Clinical Research (Date: 12.06.2020, Decision No: 09.2020.649).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: F.I.G., M.N.Y.; Design: F.I.G., M.N.Y.; Supervision: F.I.G., M.N.Y., O.S., T.S.; Materials: F.I.G.; Data collection &/or processing: F.I.G., T.S.; Analysis and/or interpretation: F.I.G., T.S.; Literature search: F.I.G., O.S.; Writing: F.I.G., O.S., T.S.; Critical review: F.I.G., O.S., T.S., M.N.Y.

Conflict of Interest

None declared.

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Kritik Durumdaki Pediatrik Hastalarda Vankomisin İlaç Düzeyleri ve Klinik Korelasyonlar

Amaç: Vankomisin, dirençli gram-pozitif enfeksiyonların tedavisinde sıklıkla kullanılan bir antibiyotiktir. Pediatrik hastalarda etkinliği ve güvenliği ile ilgili veriler sınırlı olmasına rağmen, klinik uygulamada yaygın olarak kullanılmaktadır. Önerilen serum trough (çukur) düzeyleri 15-20 mg/L, peak (zirve) düzeyleri ise 20-40 mg/L'dir. Bu hedef değerlere ulaşmak için genellikle enfeksiyon tipine göre 40-60 mg/kg/gün dozunda uygulanır. Pediatrik yoğun bakım ünitesi (PYBÜ) hastaları genellikle karmaşık klinik özellikler taşır. Bu çalışmada, ünitemizde tedavi edilen hastalarda vankomisin serum düzeylerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya, 2015-2019 yılları arasında PYBÜ'de yatan, vankomisin tedavisi alan ve serum vankomisin düzeyi ölçülen hastalar dahil edilmiştir.

Bulgular: Toplam 14 hastanın (median yaş: 45.4 ay; %42.9 erkek) verileri değerlendirildi. En sık tedavi endikasyonları sepsis (%50) ve pnömoni (%21.4) idi. Median vankomisin dozu 50 mg/kg/gün (40-60) ve tedavi süresi 7 gün (2-10) olarak saptandı. Toplam 30 serum vankomisin düzeyi analiz edildi; bunların %47.6'sı çukur ve %52.4'ü tepe düzeyleriydi. Düzeylerin %44.4'ü hedef aralıkta, %44.4'ü hedefin altında ve %11,'i hedefin üzerindeydi.

Sonuç: Kritik durumdaki pediatrik hastalarda optimal vankomisin düzeylerine ulaşmak genellikle bireyselleştirilmiş doz ayarlamaları gerektirir. Hem etkinliği hem de güvenliği sağlamak için yakın terapötik izlem esastır.

Anahtar Sözcükler: Pediatri; terapötik ilaç izlemi; vankomisin.