Therapeutic Drug Monitoring of Vancomycin Following Critical Care Illnesses: Peak Concentration Determination Maybe Critical

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Focus

Sepsis in intensive care unit (ICU) has been one of the main causes of mortality in critically ill patients. Starting effective empirical regimens as soon as possible is necessary to prevent disease progression to multiple organ failure disorder (1). The former recommended empirical regimens have mostly covered gram-negative microorganisms (2-3). However following the increase in the prevalence of gram-positive microorganisms, especially methicillin-resistant Staphylococcus aureus (MRSA), the empirical regimen should be considered to cover gram-positive microorganisms for treatment of patients (4-7). Vancomycin is a glycopeptide antibiotic wildly used to fight against serious gram-positive infections involving MRSA. Traditional dosing regimens of vancomycin was administrated 1 g every 12 hours or 15 mg/kg every 12 hours in order to set trough serum concentration of vancomycin in the range of 5-10 mg/L (8). Following the reports of increase in incidence of vancomycin-resistant S.aureus strains (VRSA) and germs with higher minimum inhibitory concentrations (MICs) for vancomycin, a huge number of studies have performed to identify the determinants that influence bacterial resistance against vancomycin. Optimum area under the time concentration curve/minimum inhibitory concentration (AUC/MIC) and a variety of trough concentration ranges has been studied. Finally the studies concluded that AUC ≥400 of vancomycin is the best factor in the success of treatment and prevention of vancomycin-resistant (4-5). Considering that the most of MRSAs still have MIC less than 1 mg/L, this trough concentration range has the best correlation with AUC of 400 mg·h/L or greater (4-7).

American Society of Health-system Pharmacists (ASHP) therapeutic guidelines recommend that “For a pathogen with an MIC of 1 mg/L, the minimum trough serum vancomycin concentration would have to be at least 15 mg/L to obtain the target AUC/MIC ≥400” (5).

Routine practice at our center for patients with normal
glomerular filtration rate (GFR) who have indication of treatment with vancomycin following sepsis is a loading dose of 25 mg/kg (based on actual body weight) at a rate of 1000 mg/hr following with 15 mg/kg every 8 hours until the individual pharmacokinetic parameters of the patient is calculated. By measuring both of trough and peak serum concentration of vancomycin in patients, we are able to calculate pharmacokinetic parameters such as elimination rate ($K_e$), volume of distribution ($V_d$), half life ($t_{1/2}$) and clearance of vancomycin ($Cl_{max}$) individually for each patient. Although there are no adequate studies on MIC at our center according to the reports of similar centers in Iran, MIC can be considered 1 mg/L approximately (9-10). We adjust the doses based on achievement AUC ≥400 mg·hr/L in divided doses every 6 to 12 hours daily and AUC can be calculated with good approximation according to AUC=Dose/CI. Despite what have been mentioned in the clinical guidelines, we have frequently observed in patients treated with vancomycin every 8 hours, with AUC of 400 mg·hr/L or greater, although the trough serum concentration has been less than 15 mg/L. According to the guidelines recommendation in this situation, if just the trough serum concentration checked, it is necessary to increase the dose of vancomycin in patients to achieve trough serum concentration above 15 mg/L (5). In other words, measuring trough serum of vancomycin alone is not an accurate estimate of AUC in critically ill patients.

Pharmacokinetic alteration of vancomycin in critically ill patients can provide imprecise correlation between trough serum concentration and AUC. Vancomycin clearance can vary proportionately with renal function (11). Volume of distribution of vancomycin is higher in patients with serum creatinine greater than 1 mg/dl (12). Some studies show that in patients with sepsis, as the systemic inflammatory response syndrome (SIRS) score increase, the vancomycin clearance increase too that is probably due to increased blood flow in the kidneys following SIRS (13). The altered pharmacokinetics of many drugs following SIRS and sepsis in critically ill patients has been often reported before (14-17). Physiological changes, fluid therapy and therapeutic interventions such as positive end-expiratory pressure (PEEP) and extracorporeal membrane oxygenation (ECMO) can affect the pharmacokinetics of drugs considerably (18-19). As a result, some of these factors can lead to the unpredictability of the relationship between trough serum concentration and AUC due to changes in volume of distribution and clearance.

Finally it should be noted that if MIC is considered about 1 mg/L or less and target AUC is 400 mg·hr/L, dose adjustments to achieve targeted trough concentration of ≥15 mg/L can lead to irrational overuse of vancomycin. So it is logical that in the hospitals with pharmaceutical care centers that have the ability to implement more advance calculations of pharmacokinetic parameters, two serum concentrations of vancomycin be measured: peak and trough. Therefore vancomycin clearance is calculated for each patient individually and dose adjustment is done based on AUC. Results of our recent study will discuss aforementioned issue in the near future.

References
