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Therapeutic Drug Monitoring of Vancomycin

Ana Luisa Robles-Piedras[1]* and Eva Hilda González-López[2]

[1]*Área Académica de Farmacia, del Instituto de Ciencias de la Salud, Universidad Autónoma del Estado de Hidalgo, México,*
[2]*Laboratorio de Química, Instituto Nacional de Cardiología Ignacio Chávez, Tlalpan, México*
E-mail: ana0536@yahoo.com

Abstract

Vancomycin, a glycopeptide antibiotic, was developed and released in the 1950's for the treatment of aerobic gram-positive infections and has been widely used mainly in the treatment of methicillin-resistant *Staphylococcus aureus* infections. Early reports regarding the possibility of nephrotoxicity and ototoxicity led to concern about the use of vancomycin and the need to monitor serum concentrations. In Mexico, the National Institute of Cardiology measures serum level of some drugs, such as vancomycin on a routine basis. Nevertheless, although a large number of measurements are made, the quantification of drug in serum is only used by physicians as a empiric parameter for dose adjustment. The aim of this work was to know whether dosing was appropriate taking the therapeutic interval as a commonly accepted baseline and to propose viable alternatives in the case dosing was inadequate. Peak and through vancomycin levels were analyzed retrospectively (n=295), in patients from 18 to 65 yr old with diagnosis of sepsis. The relationship between administered dose and measured blood levels was established. The equation that characterizes the study population was obtained based on a single compartment model considering the proportional relationship between vancomycin and creatinine clearance. The analysis shows that only 44% of C_{trough} and 47% of C_{peak} values represented therapeutic levels, with the remainder either toxic or ineffective.

Introduction

Vancomycin, a tricyclic glycopeptide antibiotic that is largely excreted unchanged in the urine, was developed and released in the 1950's for the treatment of aerobic gram-positive infections and has been widely used since in the treatment of methicillin-resistant *Staphylococcus aureus* infections [1,2]. Because of this, patients with reduced renal function have decreased vancomycin clearance and need reduced doses or increased dosing intervals. Common adverse reactions to vancomycin include hypotension, flushing, erythematous rash, and chills [3]. Moreover, effective dosing is essential to both prevent these adverse effects as well as to prevent the spread of infection from patients ineffectively treated.

The pharmacokinetics of vancomycin is thought to be straight-forward, with low protein binding, renal elimination with no metabolism, and no known pharmacogenetic problems. The volume of distribution is ~0.4 L/Kg, the clearance approximates that of the glomerular filtration rate and the half-life is ~6 hr in patients with normal renal function [4].

Vancomycin has a low therapeutic index, with nephrotoxicity and ototoxicity complicating therapy. Vancomycin, like β-lactam antibiotics, works best if the concentration at the site of activity is maintained above the minimum inhibitory concentration throughout the dose interval (so called time-dependent killing). More than 45 yr after the introduction of vancomycin for the treatment of severe antibiotic- resistant staphylococcal infections, there are still controversies regarding the determination and interpretation of vancomycin serum concentrations [4,5]. Vancomycin is mainly eliminated *via* the kidney by glomerular filtration and insufficient renal function in a patient can lead to a long elimination half-life and a high serum level of the drug increasing the risk of toxicity. In order to reduce the possibility of side effects and to maintain an effective drug concentration, recommended therapeutic windows have been reported: a peak (1 to 2 hr after the end of infusion) concentration of below 24-40 μg/mL and a through concentration of below 10 μg/mL.

To control vancomycin concentrations within these windows, therapeutic drug monitoring is useful and allows the planning of an individual optimal vancomycin dosage regimen [6]. Therapeutic drug monitoring of vancomycin has been proposed to provide the following: 1) a decreased incidence of vancomycin induced nephrotoxicity, indicating that is a cost-effective procedure, and 2) the drug works most effectively if the concentration at the site of infection is maintained above minimum inhibitory concentrations values throughout the dose interval [7,8].

Materials and Methods

We retrospectively analyzed the through and peak concentrations of vancomycin in 295 septic patients between 18 to 65 years of age. The relationship between dose and concentration of drug was established by regression analysis.

To conduct the pharmacokinetic characterization of vancomycin, the creatinine clearance was calculated using the Cockroft-Gault equation [9] and the calculations only made for those cases with normal renal function and for which serum creatinine, age, weight and height, as well as the minimum and maximum vancomycin concentrations were known (n = 65). Vancomycin clearance, the value of the elimination rate constant, and a volume of distribution of 0.7 L/kg was obtained through the application of the concept of a linear first-order kinetic single compartment model. Since vancomycin is eliminated mainly by the kidney and displays a relationship almost directly proportional to creatinine clearance, we performed an analysis that characterized the study population.

Results and Discussion

Peak and through vancomycin levels were retrospectively analyzed (n=295) in septic patients 18 to 65 years old where the dose administered and measured blood levels were established. The through plasma levels of vancomycin for patients in our study showed a great inter-individual variability (Fig. 1). When the drug plasma levels were correlated with the dose administered per patient body weight, no linear correlation was found (*r*=0.1). Some studies have suggested that trough serum vancomycin concentrations of <10 mg/L may predict therapeutic failure and the potential for the emergence of infection [10,11].

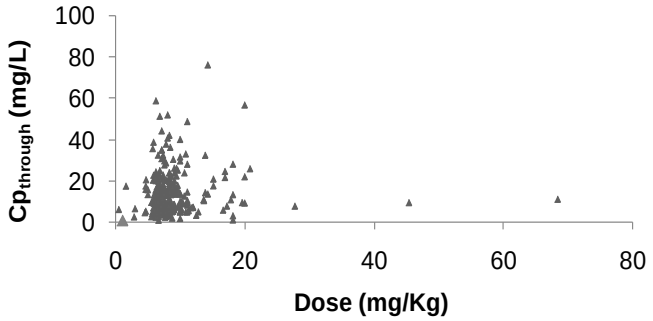

Figure 1. Relationship between vancomycin dose in milligrams per kilogram of body weight and the through vancomycin concentration measured in the patient before administering the next dose.

A large number of measurements are below the lower limit for the proposed interval for vancomycin peak concentration and some patients have values even higher than 50 mg/L (Fig. 2) which is indicative of a very high probability that the patient presented symptoms of adverse reactions and a significant possibility for toxicity since the same dose can result is very different plasma levels. To carry out the vancomycin pharmacokinetic characterization, we calculated the creatinine clearance by means of Cockroft-Gault's equation in those patients with normal renal function and for whom all information was available such as serum creatinine, age, weight and height, as well as through and peak vancomycin concentrations (n = 65). Based on the fact that vancomycin is eliminated predominantly by the kidneys in an almost direct proportion to the creatinine clearance, we established a simple first-order equation that characterized the study population.

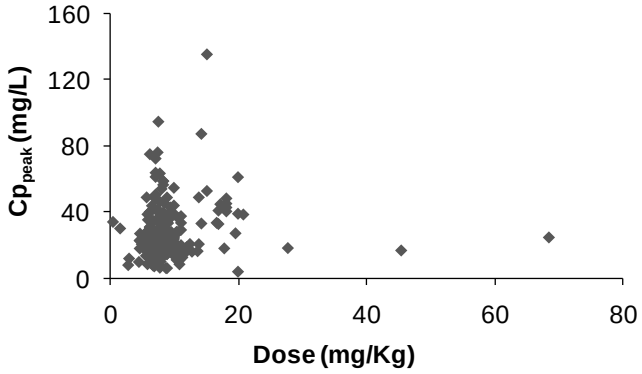

Figure 2. Relationship between the dose in milligrams per kilogram of body weight and the peak vancomycin concentration, taken before administering the next dose.

The relationship between creatinine clearance and vancomycin clearance is shown in figure 3. The data adjusted to a single compartment model, showed low correlation (*r*=0.24), the final equation that characterizes the population was $CL_{vancomycin}$ = 0.9781 $CL_{creatinine}$ (L/h) + 11.69. This study shows that only 44% of trough and 47% of peak concentrations, presented therapeutic levels leaving with this a high percentage of patients with an ineffective plasma concentration or a potentially potential toxicity one.

The benefits of therapeutic drug monitoring have been well established and are almost universally recognized. Monitoring for drugs with narrow therapeutic windows and significant inter-patient variability must include drug level monitoring. Monitoring drug levels and adjusting therapy increases the efficiency and clinical benefit of treatments while saving costs of hospitalization. In order to provide effective monitoring, parameters such as drug sampling time become critical.

Today, it is clear that therapeutic monitoring is necessary in the managing of drugs with narrow therapeutic window, for patients with complex diseases, and those taking additional drugs with a high risk to present adverse reactions.

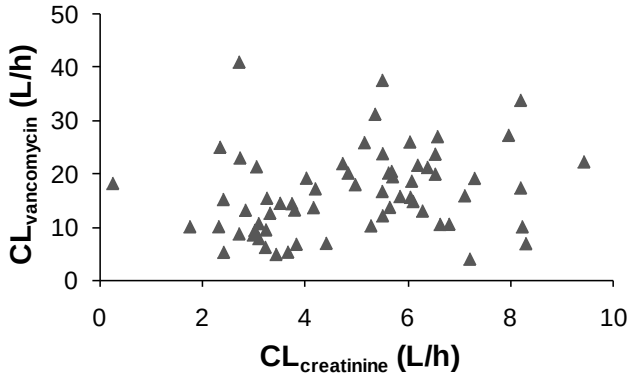

Figure 3. Relationship between vancomycin clearance and creatinine clearance in 65 patients with diagnosis of sepsis and renal normal function

We suggest that there should be a complete reappraisal of the dosage and monitoring of vancomycin. The basic cost of a single vancomycin assay is small, but if the costs of blood collection, transport to the laboratory, time spent processing paperwork, running the assay and result reporting are taken into consideration, the true costs are very high and likely exceed the costs of drug dosing. Clear guidelines are urgently required based on careful study. If better practices are established and adopted, patients will benefit. Involvement of clinical pharmacy in this effort are cost effective and should be encouraged.

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