EDITORIAL

Measuring pre- and post-dose vancomycin levels—time for a change?

Vancomycin, a glycopeptide antimicrobiotic, has been available for over 30 years. Recently, its use has increased in parallel with the increase in infections with antibiotic-resistant organisms; in particular, methicillin-resistant Staphylococcus aureus, multi-resistant S. epidermidis and enterococci. For infections caused by multi-resistant staphylococci and enterococci, and for patients allergic to penicillins, vancomycin is often the treatment of choice. The availability of simple rapid assays for monitoring serum levels has facilitated vancomycin therapy; but is monitoring levels really necessary? Perhaps the increase in the number of prescriptions for vancomycin and the inevitable associated increase in costs has provided a stimulus to re-appraise the way vancomycin is prescribed and, particularly, the need to measure serum concentrations routinely. Furthermore, teicoplanin, a new glycopeptide antimicrobial, is a major rival to vancomycin in the treatment of serious gram-positive infections, and has been marketed without recommendations to monitor serum levels for uncomplicated infections.1

At issue is whether vancomycin levels need to be monitored at all for the treatment of uncomplicated infections in patients with normal or near normal renal function. Supplementary questions surround the types of patients who might require monitoring and whether both pre-dose and post-dose levels are of value. The main criterion for monitoring serum drug concentrations is to ensure enough drug is given for efficacy, whilst avoiding concentrations associated with a significant risk of toxicity. The need for monitoring is emphasised if there is patient variation in drug pharmokinetics so dosing cannot be predicted reliably from nomograms. For vancomycin, the need for careful monitoring has always been accepted on the basis that these criteria are fulfilled. However, this has been challenged recently.

Originally, in the late 1950s, it was suggested that serum vancomycin levels be monitored in all patients on parenteral therapy to avoid the toxicity seen in patients with serum levels > 80 mg/L.2 Since that time it has become accepted clinical practice to measure trough and peak concentrations in the same way that aminoglycoside levels are measured. However, the pharmacokinetic and bactericidal characteristics of these agents are quite different. Unlike aminoglycosides, which depend on a high peak level to improve bactericidal activity (concentration-dependent killing), vancomycin bactericidal activity is saturated at a relatively low concentration, and is dependent on duration of exposure to the organism (time-dependent killing).3 Concentration-dependent killing by vancomycin has not been demonstrated against staphylococci.4 Therefore, high peak vancomycin concentrations do not correlate with increased bactericidal activity, and measuring levels to ensure an adequate "peak" level is unnecessary.

Adverse reactions to vancomycin such as the red man syndrome, other rashes and neutropenia are not dose dependent, and are not preventable by drug monitoring. Vancomycin-associated otoxicity was associated originally with serum levels > 80 mg/L, and it was recommended that concentrations > 50 mg/L be avoided.2 However, the evidence for vancomycin-induced toxicity has now been questioned.5 Data are scarce but suggest that if otoxicity is associated with vancomycin, it is with very high serum levels (> 80 mg/L).6 Vancomycin is also associated with nephrotoxicity, but an extensive review of the available data suggests that nephrotoxicity, which is reversible, probably occurs in < 5% of patients who are treated with vancomycin alone.5 However, when vancomycin is given in combination with other nephrotoxic agents, particularly aminoglycosides, the incidence may rise to c. 35%.7 It is unclear whether toxicity is proportional to serum concentration; although pre-dose vancomycin concentrations of > 10 mg/L have been associated with nephrotoxicity, this has not been confirmed in other studies. When reviewing cases it is difficult to establish with certainty whether vancomycin is the cause of impaired renal function or whether vancomycin accumulation has occurred as a consequence of decreased renal function for other reasons; any process causing glomerular damage will result in a reduction in vancomycin excretion and drug accumulation. Despite its clinical use for over 30 years, there are few clinical data on vancomycin efficacy. An empirical dose of 2 g/day was chosen on the basis that this achieved "satisfactory" serum levels, but lower doses may be just as effective; staphylococcal endocarditis has been treated successfully with 1 g/day.8

An often quoted rough guide is that the trough level of an antibiotic should exceed the minimum inhibitory concentration (MIC) for the infecting organism. For vancomycin, this would be c. 1-5 mg/L or less for most susceptible pathogens; but as vancomycin is c. 50% protein bound, trough levels of 4-5 mg/L would be
needed to maintain antibacterial efficacy (as only free drug is active). Others have proposed that serum levels titrated against minimum bacterial concentrations are more meaningful, particularly when treating enterococcal infections, and suggest a bactericidal serum titre of > 8 (i.e., > 12 mg/L for vancomycin).8

Another important factor in determining dosing regimens is the concentration of drug achievable at the site of infection. Studies have shown that vancomycin is widely distributed in body fluids (except cerebrospinal fluid and aqueous humour) and levels are adequate to treat most infections, with concentrations in the range 40–130% of the serum level.10

Vancomycin is excreted almost exclusively via the kidneys and there is a direct correlation between vancomycin clearance and creatinine clearance. Nomograms have been revised to predict the dose of vancomycin that would produce pre- and post-dose levels within accepted target ranges,11 or a steady state serum concentration of 15 mg/L,12 from a revised value for creatinine clearance based on age, sex, weight and serum creatinine. The success of these nomograms has been variable13,14 and they may not be reliable enough to predict vancomycin levels in all patients.

Another controversial aspect of monitoring vancomycin is the timing of the post-dose level. The manufacturers recommend sampling 2 h after completion of the infusion15 as levels taken earlier may be misleading because of the large variations occurring during the distribution phase. Even in patients with normal renal function there is a large variation in the volume of distribution and clearance of vancomycin. However, recommendations have varied from 15 min to > 2 h post-dose, making direct comparisons of studies reporting vancomycin concentrations difficult. The pharmacokinetics of vancomycin follow a 2–3 compartment model with the end of the distribution phase at c. 2 h, and the vancomycin concentration at 1 hr may be more than double that taken at 2 h and still be within the recommended target ranges of 25–40 mg/L and 18–26 mg/L, respectively. Therefore, accurate timing of the post-dose level is critical to interpretation. On busy wards, timing of post-dose levels must inevitably be compromised, limiting their value. Abandoning the measurement of post-dose vancomycin concentrations would eliminate the controversy surrounding their interpretation. Saunders18 has suggested that, provided the pre-dose concentration is within recommended limits (< 10 mg/L) and certainly < 15 mg/L, the post-dose level (taken at 1-h) is unlikely to fall into a potentially toxic range (> 40 mg/L). A review of our own data on vancomycin monitoring supports this view; high post-dose levels were associated with high pre-dose levels (> 10 mg/L), and, therefore, the pre-dose level alone prompted dose adjustment.

It has been proposed that, in uncomplicated cases, neither the measurement of pre- or post-dose vancomycin levels is necessary at all;4,19 but what constitutes an uncomplicated case? Many of the patients on vancomycin therapy are critically ill, receiving other potentially nephrotoxic agents or are at risk of developing renal impairment; in these patients we would support monitoring of vancomycin levels to avoid vancomycin accumulation. Other indications include patients on haemodialysis (who may only require one dose of vancomycin per week), those not responding to apparently appropriate therapy, or when the infecting organism has an unusually high MIC to vancomycin.

The basis on which the practice of measuring serum vancomycin levels as a means of monitoring therapy has been re-examined. Although questions remain concerning the optimal serum concentrations of vancomycin to predict efficacy and minimal toxicity, the case for routine measurement of post-dose concentrations is weak, with no additional information over determining a pre-dose concentration alone. We would support measurement of a pre-dose concentration in patients receiving vancomycin therapy to monitor for drug accumulation, particularly in "at risk" patients. Before routine measurement of levels is abandoned altogether, trials are needed to define target serum levels more accurately, maximising efficacy and minimising toxicity, and to define the incidence of toxicity and nephrotoxicity and their relationship to serum vancomycin concentrations.

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