Guidelines Review

Therapeutic Monitoring of Vancomycin in Adult Patients: A Consensus Review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

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Introduction

Vancomycin, a glycopeptide antibiotic, is the first line agent in the treatment of penicillinase-producing strains of *Staphylococcus aureus* and is increasingly used in Australian hospitals in the empiric treatment of sepsis. The emergence of vancomycin-resistant enterococci, and more recently vancomycin-resistant *Staphylococcus aureus*, is of particular concern. Under-dosing contributes to vancomycin resistance and ineffective treatment while over-dosing is associated with toxicity.[1] Optimising vancomycin therapy with therapeutic drug monitoring (TDM) is therefore widely recommended. However, the interpretation of serum concentrations and the relevant evidence base has been the subject of debate.

Recently, a thorough and comprehensive American consensus review on the therapeutic monitoring of vancomycin was published (the Review).[2] The Review provides a series of summaries and recommendations with detailed supporting discussion and description of the level of evidence for the statements. There are no Australia-wide guidelines for TDM although advice on aspects of TDM is included in documents such as the Australian Medicine Handbook (AMH),[3] Therapeutics Guidelines (TG) Version 13[4] and local or state-wide Drug Formularies. In this manuscript we examine the recommendations of the Review (given in italics below) in the context of Australian practice. For further details we recommend reading the original Review.[2]

Recommended TDM Parameters

Optimal Monitoring Parameter

- *Trough serum vancomycin concentrations are the most accurate and practical method for monitoring efficacy.*

Traditionally vancomycin was believed to display time-dependent bacterial killing, in which case there is little evidence for the use of target peak concentrations. Similarly, this is not recommended in the TG or the AMH. However, the authors have noted that several laboratories in Australia continue to recommend this measurement. Recently, as highlighted in the recommendations, there is support for a degree of concentration-dependent killing with vancomycin. However whether peak concentration or time above some multiple of the trough is the optimal measurement is currently an area of active discussion amongst infectious diseases specialists.

Timing of Monitoring

- *Troughs should be obtained just prior to the next dose at steady-state conditions (approximately after the fourth dose).*

The recommendation for trough measurements is based on the use of twice or three times daily dosing. The timing of sampling in the American Guidelines (after four doses) is based on time to reach steady state. It differs from the TG

where sampling after the first dose is recommended, unless patients have a glomerular filtration rate (GFR) <10 mL/min in which case sampling is at 48 h. This may be useful in avoiding toxicity if this is of concern, but is less relevant for ensuring adequate mean inhibitory concentration (MIC) which is affected by the time to redistribute to tissues where the antimicrobial activity is required.

Optimal Trough Concentration

- *Minimum serum vancomycin trough concentrations should always be maintained above 10 mg/L to avoid development of resistance. For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg/L to generate the target AUC (Area under the curve):MIC of 400.*

The TG recommendations have been adopted in many Australian laboratories covering differing ages, differing infectious conditions and usually without MIC values being recommended. Of note, the TG provide different trough concentration recommendations for 6 and 12 hourly dosing (15–25 mg/L and 10–20 mg/L respectively), which is not concordant with current clinical practice.

It should be noted that as there are factors about both the patient (e.g. site and source of infection, pharmacokinetic parameters such as clearance and volume of distribution) and the organism (type and MIC), vancomycin concentrations should be interpreted as a guide only. For example, with pneumonia or osteomyelitis, the exact concentration at the site of infection will be unknown. However, it is reasonable to assume that the higher the trough concentration, the greater the likelihood that the concentration in extravascular sites of infection is going to be above the MIC. Thus a higher trough concentration may be required for some infections.

Optimal Trough Concentration for Complicated Infections

- *Vancomycin serum trough concentrations of 15–20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations and improve clinical outcomes.*

Complicated infections are those associated with endocarditis, osteomyelitis, meningitis and hospital acquired pneumonia caused by *Staphylococcus aureus.* These recommendations are echoed in the TG[4] with the additional note that the reason for monitoring patients with aggressive dosing is to reduce the risk of developing resistant strains of MRSA. The TG add that monitoring should be undertaken in patients with renal impairment or abnormal volumes of distribution (e.g. burns, oedema). The AMH states that measurement is unnecessary in most cases but that concentrations can enable dose individualisation (a) when vancomycin is given with an aminoglycoside; (b) in people with altered pharmacokinetics (e.g. burns, morbidly obese); (c) in patients on haemodialysis receiving infrequent doses of vancomycin (as half-life varies according to ultrafiltration rate and dialyser pore size) or (d) during high dose and/or prolonged treatment in patients with unstable or impaired renal function. Patients on haemodialysis and the obese are two groups frequently forgotten when it comes to dose individualisation.[5]

Dosing Regimen

Dosing to Achieve Optimal Trough Concentrations

- *Daily doses of 15–20 mg/kg (as actual body weight) given every 8–12 h are recommended for most patients with normal renal function to achieve the suggested serum concentrations when the MIC is ≤1 mg/L. In patients with normal renal function, the targeted AUC:MIC of >400 is not achievable with conventional dosing methods if the MIC is ≥2 mg/L in a patient with normal renal function.*

Loading Doses – Complicated Infections

- *In seriously ill patients, a loading dose of 25–30 mg/kg (based on actual body weight) can be used to facilitate rapid attainment of target trough serum vancomycin concentration.*

There has been recent support for loading doses of vancomycin, so that concentrations above MIC are quickly attained, therefore providing therapeutic AUC/MIC exposures earlier.[6]

Continuous vs Intermittent Dosing

- *Continuous infusion regimens are unlikely to substantially improve patient outcomes when compared to intermittent infusions.*

The Review specifies that continuous infusion is unlikely to add any additional benefit which is in agreement with clinical practice and the TG. However this lack of recommendation for continuous infusion vs 12 or 8 hourly bolus dosing may be due to deficient rather than negative evidence. For example, vancomycin is predominantly a time-dependent antibiotic so it is probable that continuous infusion provides at least the same benefit. Recent evidence suggests that efficacy is not determined by frequency of administration (i.e. 24 h continuous vs bolus dosing)[7] although a small study has suggested that the percentage of time that the vancomycin concentration at the biophase (e.g. alveolar space, heart valve) is above the MIC can be optimised using continuous infusion.[8]

TDM for Vancomycin-Induced Nephrotoxicity

Definition: A minimum of two or three consecutive

documented increases in serum creatinine concentrations (defined as an increase of 45 µmol/L or a ≥50% increase from baseline, whichever is greater) after several days of vancomycin therapy.[2]

Criteria for Monitoring

- *Data do not support using peak serum vancomycin concentrations to monitor for nephrotoxicity.*
- *Trough monitoring is recommended for patients receiving aggressive dosing (i.e. to achieve sustained trough levels of 15–20 mg/L) and all patients at high risk of nephrotoxicity (e.g. patients receiving concurrent nephrotoxins).*
- *Monitoring is also recommended for patients with unstable (i.e. deteriorating or significantly improving) renal function and those receiving prolonged courses of therapy (more than three to five days).*

There are limited data suggesting a direct causal relationship between toxicity and specific serum vancomycin concentrations. In addition, data are conflicting and characterised by the presence of confounding nephrotoxic agents, inconsistent and highly variable definitions of toxicity, and the inability to examine the time sequence of events surrounding changes in renal function secondary to vancomycin exposure. There is very little evidence of nephrotoxicity or ototoxicity with vancomycin used alone. The perception may stem from the past where impurities with the vancomycin caused toxicity. However vancomycin can certainly potentiate the nephrotoxicity of other drugs such as aminoglycosides if given concurrently. Currently available data has suggested that vancomycin nephrotoxicity can occur at doses above 4 g/day[9] or with average steady state concentrations above 28 mg/L.[1]

Vancomycin is renally cleared, so the dose needs to be adjusted as the GFR changes. In the absence of a measured GFR, current recommendations suggest using Cockcroft-Gault estimations to adjust the dose.[3] Changes in vancomycin concentrations when the dose has remained unchanged are a reliable early indicator of changes in GFR. The definition of vancomycin-induced nephrotoxicity is a reminder that monitoring creatinine is a part of TDM for vancomycin.

Frequency of Monitoring

- *Frequent monitoring (more than one trough before the fourth dose) for short course or lower intensity dosing (to attain target trough concentrations below 15 mg/L) is not recommended.*
- *All patients on prolonged courses of vancomycin (exceeding three to five days) should have at least one steady-state trough concentration obtained no earlier than at steady state (following the fourth dose) and then repeated as deemed clinically appropriate.*
- *There are limited data supporting the safety of sustained trough concentrations of 15–20 mg/L. Clinical judgment should guide the frequency of trough monitoring when the target trough is in this range. Once-weekly monitoring is recommended for haemodynamically stable patients. More frequent or daily trough monitoring is advisable in patients who are haemodynamically unstable.*

In patients with unstable renal function and/or uncertain clinical response, monitoring may need to be more frequent. In patients with satisfactory clinical response, stable renal function and trough concentrations within the desired therapeutic range, repeat monitoring should not need to be more frequent than twice-weekly. The most significant determinant of vancomycin clearance is GFR and therefore, changes in serum creatinine can indicate the need for TDM to determine if dose adjustment is indicated.

Trough concentrations should normally be checked prior to one of the third, fourth or fifth dose after commencement, after change in dose or change in renal function, or after 48 h if GFR is <10 mL/min.

TDM for Vancomycin-Induced Ototoxicity

Criteria for Monitoring

- *Monitoring for ototoxicity is not recommended for patients receiving vancomycin monotherapy.*
- *Monitoring should be considered for patients receiving additional ototoxic agents such as aminoglycosides.*

See the section on monitoring of nephrotoxicity for additional comments.

Summary

The Review is a welcome and up-to-date consensus statement on the use of vancomycin. Although many of the points are pertinent to Australasian practice, the clinical context may be subtly different such that different recommendations apply here. It is thus an apt time for clinical, biochemical, pharmacological and pathology staff in Australasia to collaborate and discuss the literature with particular relevance to establishing guidelines for an Australasian context. The new TG (Version 14) will be an interesting update in the antibiotic TDM area and we hope it will be used as a springboard for Australasian clinical research into this area.

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