

Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists

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Practice guidelines for therapeutic monitoring of vancomycin treatment for *Staphylococcus aureus* infection in adult patients were reviewed by an expert panel of the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. A literature review of existing evidence regarding vancomycin dosing and monitoring of serum concentrations, in addition to patient outcomes combined with expert opinion regarding the drug's pharmacokinetic, pharmacodynamic, and safety record, resulted in new recommendations for targeting and adjustment of vancomycin therapy.

EXECUTIVE SUMMARY

Adjustment and targeting of specific serum concentrations of vancomycin in patients have been the subject of debate for many years. The primary premise for monitoring and adjustment of serum vancomycin concentrations is based on the perceived need to achieve serum concentrations at some multiple above the minimum inhibitory concentration (MIC) for the offending organisms and the avoidance of potential adverse effects, such as ototoxicity or nephrotoxicity. The lack

of well-designed randomized clinical evaluations or data to support a clear relationship between specific serum concentrations and patient outcome has been the overriding contributor to this controversy. Unfortunately, the controversy has resulted in variable clinical practice methods. In some cases, monitoring is infrequent or avoided. In other cases, monitoring and dosage adjustment is overly aggressive.

The relationship between serum concentrations and treatment success or failure in serious *Staphylococcus aureus* infections has recently been established. Failure rates exceeding 60% for *S. aureus* displaying a vancomycin MIC value of 4 mg/L prompted recommendations in 2006 from the Clinical and Laboratory Standards Institute to lower the breakpoint for susceptibility from 4 to 2 mg/L and in 2008 from the US Food and Drug Administration. Recently, a number of studies have established a relationship between vancomycin treatment failures and infections in patients with methicillin-resistant *S. aureus* displaying an MIC of

Received 9 April 2009; accepted 10 April 2009; electronically published 1 July 2009.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

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Clinical Infectious Diseases 2009;49:325–7

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1058-4838/2009/4903-0001\$15.00

DOI: 10.1086/600877

2 mg/L. Vancomycin displays concentration-independent activity against *S. aureus*, with the area under the concentration curve (AUC) divided by the MIC as the primary predictive pharmacodynamic parameter for efficacy. On the basis of in vitro, animal, and limited human data, an AUC/MIC value of 400 has been established as the pharmacokinetic-pharmacodynamic target. To achieve this target, larger vancomycin doses and high trough serum concentrations are required. Although vancomycin administration is associated with some adverse effects, the committee felt that the potential benefit of increased drug dosage was worth the risk of mostly reversible adverse events.

LITERATURE REVIEW, ANALYSIS, AND CONSENSUS

The expert panel reviewed the literature on pharmacokinetics, pharmacodynamics, efficacy, resistance, and toxicity of vancomycin.[1] A computerized literature search of PubMed for all relevant data published in the English language from 1958 through 2008 was conducted and forms the basis of these recommendations. The quality of the studies was rated, and consensus recommendations were graded using the classification scheme of the Canadian Medical Association (table 1). It should be noted that the majority of the published vancomycin-monitoring studies were not randomized but consisted of observational data. In addition, data from pediatric studies were not included; therefore, the recommendations are only for adult patients. The committee members were assigned specific topic areas and met via several teleconferences and in person to review the draft guidelines. The draft monitoring guidelines were circulated among committee members and were reviewed by each participating professional society for comments and re-

visions. The final guidelines were reviewed and approved by the 3 supporting organizations.

SUMMARY OF RECOMMENDATIONS

Therapeutic Vancomycin Dose Adjustment and Drug Monitoring

Dosage. Initial vancomycin dosages should be calculated on the basis of actual body weight, including for obese patients. Subsequent dosage adjustments should be based on actual serum concentrations, to achieve targeted therapeutic concentrations. Continuous infusion regimens are unlikely to substantially improve patient outcome, compared with intermittent dosing. (Level of evidence, II; grade of recommendation, A.)

Peak versus trough concentrations. Trough serum vancomycin concentrations are the most accurate and practical method of monitoring the effectiveness of vancomycin. Trough serum concentrations should be obtained just before the fourth dose, at steady-state conditions. (Note that steady-state achievement is variable but occurs approximately just before the fourth dose.) (Level of evidence, II; grade of recommendation, B.)

Avoidance of development of resistance. On the basis of the evidence suggesting that *S. aureus* exposure to trough serum concentrations of <10 mg/L can produce strains with vancomycin-intermediately susceptible *S. aureus* (VISA)-like characteristics, it is recommended that trough serum vancomycin concentrations always be maintained at >10 mg/L to avoid the development of resistance. (Level of evidence, III; grade of recommendation, B.)

Recommended trough serum concentrations and dosage adjustments. On the basis of the potential to improve penetration, to increase the probability of optimal target serum concentrations, and to improve clinical outcomes of complicated infections, such as bacteremia, endocarditis, osteomyelitis,

Table 1. Definition of quality of evidence and strength of recommendation.

Assessment	Type of evidence
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
Strength of recommendation	
Grade A	Good evidence to support a recommendation for use
Grade B	Moderate evidence to support a recommendation for use
Grade C	Poor evidence to support a recommendation

NOTE. Adapted from the Canadian Task Force on the Periodic Health Examination [2].

meningitis, and hospital-acquired pneumonia caused by *S. aureus*, trough serum vancomycin concentrations of 15–20 mg/L are recommended. Trough serum vancomycin concentrations in that range should achieve an AUC/MIC of >400 for most patients if the MIC is <1 mg/L. (Level of evidence, III; grade of recommendation, B.) To achieve rapid attainment of this target concentration for seriously ill patients, a loading dose of 25–30 mg/kg (based on actual body weight) can be considered. (Level of evidence, III; grade of recommendation, B.) A targeted AUC/MIC of >400 is not achievable with conventional dosing methods if the vancomycin MIC is \geq 2 mg/L for a patient with normal renal function (i.e., creatinine clearance, 70–100 mL/min). Therefore, alternative therapies should be considered. Vancomycin dosages of 15–20 mg/kg (based on actual body weight) given every 8–12 h are required for most patients with normal renal function to achieve the suggested trough serum concentrations when the MIC is <1 mg/L. It should be noted that currently available nomograms were not developed to achieve these targeted end points. Individual pharmacokinetic adjustments and verification of achievement of target serum concentrations are recommended. When individual doses exceed 1 g (e.g., 1.5 and 2 g), the infusion period should be extended to 1.5–2 h. (Level of evidence, III; grade of recommendation, B.)

Vancomycin toxicity. There are limited data suggesting a direct causal relationship between toxicity and specific serum vancomycin concentrations. There are also conflicting data characterized by 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. A patient should be considered to have vancomycin-induced nephrotoxicity if multiple (at least 2 or 3 consecutive) high serum creatinine concentrations (increase of 0.5 mg/dL or >50% increase from baseline, whichever is greater) are documented after several days of vancomycin therapy in the absence of an alternative explanation. (Level of evidence, II; grade of recommendation, B.)

Monitoring of serum concentrations to reduce toxicity. Available evidence does not support monitoring of peak serum vancomycin concentrations to decrease the frequency of nephrotoxicity. (Level of evidence, I; grade of recommendation, A.) Monitoring of trough serum vancomycin concentrations to reduce nephrotoxicity is best suited for patients receiving aggressive dose targeting to produce sustained trough serum concentrations of 15–20 mg/L or who are at risk of toxicity, such as patients receiving concurrent treatment with nephrotoxins. (Level of evidence, III; grade of recommendation, B.) Monitoring is also recommended for patients with unstable renal function (either deteriorating or significantly improving

function) and for patients receiving prolonged courses of therapy (>3–5 days). (Level of evidence, II; grade of recommendation, B.) All patients receiving prolonged courses of vancomycin treatment should have at least 1 steady-state trough serum concentration measured just before the fourth dose. Frequent monitoring (>1 measurement of trough concentration before the fourth dose) for short-course therapy (<5 days) or for lower-intensity dosing (targeted to attain trough serum vancomycin concentrations of <15 mg/L) is not recommended. (Level of evidence, II; grade of recommendation, B.) There are limited data to support the safety of sustained trough serum vancomycin concentrations of 15–20 mg/L. When this target range is desired, once-weekly measurements of trough concentrations for hemodynamically stable patients is recommended. Frequent (in some instances, daily) monitoring of trough concentrations is advisable to prevent toxicity in hemodynamically unstable patients. The exact frequency of monitoring is often a matter of clinical judgment. (Level of evidence, III; grade of recommendation, B.) Data on comparative vancomycin toxicity for continuous versus intermittent administration are conflicting, and no recommendation can be made. Monitoring of serum vancomycin concentrations to prevent ototoxicity is not recommended, because this toxicity is rarely associated with monotherapy and does not correlate with serum vancomycin concentrations. Monitoring may be more important when other ototoxic agents, such as aminoglycosides, are administered. (Level of evidence, III; grade of recommendation, B.)

Acknowledgments

Potential conflicts of interest. M.J.R. received research grants from Astellas, Cubist, Forest, and Pfizer; consulted for Astellas, Cubist, Forest, Ortho-McNeil, and Targanta; and has served on speakers' bureaus for Cubist, Wyeth, Pfizer, and Targanta. J.C.R. has received research grants from Ortho-McNeil and Astra-Zeneca; has been a consultant for Ortho-McNeil, Schering, Cubist, Wyeth, Pfizer, Theravance, Optimer, and Bayer; and has served on speakers' bureaus for Ortho-McNeil, Schering, Pfizer, Wyeth, and Cubist. R.C.M. was a former consultant for Eli Lilly. W.A.C. has received research funding from Johnson & Johnson and Astra-Zeneca and has been a consultant for Bristol-Myers Squibb and Forest Pharmaceuticals. M.B. has received research funding from Cubist and has served on speakers' bureaus for Sanofi-Pasteur, Pfizer, and Ortho-McNeil. J.R.D. has received a consulting fee to testify on Capitol Hill regarding the clinical impact of the methicillin-resistant *S. aureus* outbreak in the United States; no product-specific data were discussed. B.M.L. and D.P.L.: no conflicts.

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