Vol. 34 No. 12 - Dec. 2005

drug therapy topics

ISSN 0882-6684

Harborview Medical Center / Seattle Cancer Care Alliance / University of Washington Medical Center

Editor's Note: *The Infectious Diseases (ID) Subcommittee, a standing subcommittee of the UWMC/HMC Pharmacy* and Therapeutics Committee, is charged with addressing educational issues related to the rational use of antibiotics within the setting of the UW Academic Medical Center. Chaired by Thomas (M.) Hooton, M.D., Subcommittee *membership consists of Infectious Disease Service physicians and pharmacists drawn from UW Medicine, the Seattle Cancer Care Alliance, the Department of Pharmacy Services, and the UW School of Pharmacy.*

Infectious Diseases Subcommittee

Special Report: Recommendations for Vancomycin Serum Concentration Monitoring in Adults

by Doug Black, Pharm.D.

Goal

The purpose of this document is to provide literature-supported recommendations for monitoring vancomycin serum concentrations in patients treated at UW Medicine.

Background

Vancomycin has long been considered a nephrotoxic and ototoxic agent. Impurities in the original vancomycin formulation were thought to have contributed significantly to the incidence of toxicity. As the purity of the commercial product has improved, reports of toxicity have declined. Nonetheless, vancomycin serum concentrations are commonly obtained in an attempt to maximize drug effectiveness while minimizing adverse effects. It is important to understand that the "therapeutic range" of vancomycin is essentially theoretical.

The vancomycin susceptibility breakpoint for staphylococci and enterococci is 4µg/mL; most strains encountered clinically have MICs under 1–2µg/mL. Given that vancomycin exhibits concentration-independent bactericidal activity and protein binding is 10–62%, a minimum desirable trough concentration of 5–10µg/mL has been suggested and generally adopted by clinicians.

A peak concentration of 20–40µg/mL follows because the volume of distribution of vancomycin is 0.5–0.9L/kg; in a 70kg patient, 1000mg of vancomycin distributed into 35-63L would boost the trough concentration about 15–30µg/mL. Measurements of peak concentrations vary as the timing of the blood draw varies. Papers published in the literature employ a wide range of peak sampling times, and yet the same peak reference range of 20–40µg/mL is used.

The original 1958 paper by Geraci et al., proposing the monitoring of serum concentrations to avoid ototoxicity was based on two occurrences of toxicity in patients with concentrations above 80µg/mL. Repetitive citing of this reference has contributed to the establishment of the "therapeutic range." The risk of nephrotoxicity is widely thought to be minimized by maintaining serum concentrations within the therapeutic range.

Hetero-resistant strains of *S. aureus* (hGISA) present with vancomycin MICs in the susceptible range of 1–4µg/mL that may increase significantly when exposed to vancomycin. Some investigators have found that low concentrations of vancomycin promote the emergence of hGISA or GISA, suggesting that the currently accepted trough reference range may be inadequate. Although there are insufficient data at this time to recommend increasing the vancomycin trough reference range beyond 5–10µg/mL, the use of a higher range may be appropriate in certain clinical situations.

Criteria for monitoring drug concentrations

For serum concentration monitoring of any drug to be rational, at least four criteria

(see below) must be met. In the case of vancomycin, only the latter two criteria are met.

1. There must be a known correlation between concentration and efficacy and/or toxicity (not so for vancomycin, see below);
2. Drug pharmacokinetics must be difficult to predict, and significant intersubject variability in drug pharmacokinetics must exist (not so for vancomycin, see below);
3. Efficacy or toxicity must be difficult to measure, or at least delayed in presentation (true for vancomycin);
4. A reliable drug concentration assay must exist (true for vancomycin).

The pharmacokinetics of vancomycin are relatively simple and predictable (moderately low protein binding, renal elimination with essentially no metabolism, no pharmacogenetic considerations). Vancomycin clearance is related to creatinine clearance in a linear fashion, as described by the following equation:

vancomycin clearance (in mL/min/kg) = 0.695 x CrCl (in mL/min/kg) + 0.05.

The linear correlation of vancomycin clearance with creatinine clearance gave rise to the Moellering dosing nomogram, published in 1981, which was designed to achieve a mean vancomycin concentration of 15µg/mL. A number of additional dosing nomograms have since been created, but none is clearly superior. Serum concentration forecasting approaches using Bayesian methods have been studied and may also yield accurate predictions of serum concentration. Regardless, key to successfully dosing vancomycin is having an accurate estimate of a patient's renal function. Therefore, in patients for whom accurate predictions of creatinine clearance are not possible, serum vancomycin concentration monitoring might be helpful. It should be noted that crystalline degradation products of vancomycin accumulate in uremia and are known to interfere with certain types of vancomycin assays; however, this is not an issue with the UW Medicine assay.

Published data, 1958-1994, reviewed in 1994 by Cantu

A comprehensive review of the vancomycin serum concentration monitoring literature was published in 1994 by Cantu et al., and summarized here. Many studies published from 1958-1994 demonstrate the effectiveness of vancomycin at fixed dosage (7.5mg/kg IV q 6h or 1g IV q 12h) for the treatment of various gram-positive infections. Peak and trough concentrations in these studies range from 18–47µg/mL and 2–13µg/mL, respectively. There is some variability due to differences in sampling time. No consistent correlations between drug concentration and clinical response are apparent.

- 167 patients exhibiting nephrotoxicity possibly associated with vancomycin are described. 82 of these patients are discussed in case reports. In 41 of the case reports, aminoglycosides were used before or concurrently with the vancomycin, and in an additional 38 there were additional factors casting doubt on the causal role of vancomycin (such as inadequate or absent description of concomitant drug use).

- The remaining 85 patients with possible nephrotoxicity are described in nine clinical studies (6 prospective, 3 retrospective). Many of these studies involve the concomitant use of aminoglycosides. In the studies that most effectively control for confounding factors, the incidence of vancomycin-associated nephrotoxicity is approximately 5% (similar to what is commonly ascribed to β-lactam therapy).

- Establishing cause and effect is difficult. Because vancomycin is renally excreted, it is difficult to conclusively determine if elevated vancomycin concentrations are the cause of nephrotoxicity or the result of a decrease in glomerular filtration secondary to some other cause. Trough concentrations above 10µg/mL are associated with nephrotoxicity by some authors but not others.

- Although it has been suggested that early preparations of vancomycin were nephrotoxic (and ototoxic) by virtue of impurities, the toxicity of these impurities is not proven, according to the drug manufacturer.

- 53 reports of tinnitus or hearing loss associated with vancomycin are described. In 36 cases, other potentially ototoxic agents were administered concomitantly. In 3 of the remaining 17 cases, patients were being treated for pneumococcal meningitis. In the cases of vancomycin monotherapy not confounded by disease state, vancomycin concentrations ranged from 17 to 62µg/mL. In all 53 instances, ototoxicity was fully reversible.

Summary of studies published, 1994-2005

Since the publication of the review by Cantu et al., in 1994, 16 relevant studies have appeared in the literature and are summarized in Table I. Several observations emerge from these recent studies:

1. No consistent relationship between serum concentrations of vancomycin and therapeutic outcome is evident.

2. If serum concentration monitoring is deemed necessary, trough vancomycin concentrations are adequate. Monitoring peak vancomycin concentrations does not offer additional benefit.

3. In general, a cause-and-effect relationship between elevated vancomycin concentrations and nephrotoxicity is difficult to establish, although two prospective studies suggest that therapeutic drug monitoring of vancomycin results in lower trough concentrations and less nephrotoxicity.

4. Reduced drug concentration monitoring leads to less expensive patient care. (The current charge for a vancomycin level for a UW Medicine inpatient is $18.93.)

Table I: Summary of Studies, 1994 - 2005

Study	Study population	Study design	Methodology	Efficacy outcomes	Toxicity outcomes
Welty et al. (1994)	Patients receiving empiric vancomycin for various infections (n=116)	Prospective, consecutive	Therapeutic drug monitoring (TDM) *vs.* non-TDM	TDM patients: less vancomycin used, shorter treatment duration, shorter length of stay	Less nephrotoxicity in the TDM group
Saunders (1994)	No details provided (n=62)	Prospective	165 peak/trough pairs collected	Mean increase in vancomycin peak from trough: 16µg/mL No patient with a trough ≤15µg/mL had a peak >40µg/mL	None
Mulhern et al. (1995)	Peritoneal dialysis patients receiving weekly IV vancomycin for peritonitis (n=31)	Retrospective	Chart review	Only predictors for relapse: day 7 trough <9µg/mL, day 28 trough <12µg/mL (all relapses successfully treated with day 28 trough = 14.7µg/mL)	None
Zimmerman et al. (1995)	Gram-positive bacteremia (n=273)	Retrospective	Chart review	Patients with peaks >20µg/mL or troughs >10µg/mL more likely to be afebrile by day 3; if trough >10µg/mL, WBC more likely normal by day 3; no association of peaks or troughs with mortality	Mean troughs: 23.2µg/mL in nephrotoxic patients *vs.* 10.2µg/mL in nonnephrotoxic patients
Kremery et al. (1996)	Febrile, neutropenic cancer patients (n=198)	Retrospective	Chart review	Not assessed	Vancomycin did not increase amphotericin B or aminoglycoside nephrotoxicity; patients with peaks >50µg/mL or troughs >10µg/mL experienced more nephrotoxicity
De Gatta et al. (1996)	Febrile, neutropenic cancer patients (n=70)	Prospective, randomized	Therapeutic drug monitoring (TDM) *vs.* non-TDM	No difference	Less nephrotoxicity in the TDM group
Bernard et al. (1997)	Gram-positive bone infection (n=15)	Prospective, uncontrolled	Continuous infusion vancomycin maintained at 25-35µg/mL, mean 6.2 months	10 patients judged to be cures	Tinnitus (2 patients), mild transient increase in creatinine (3 patients)
Kralovicova et al. (1997)	Oncology patients (n=198)	Retrospective	Peak and trough study	Neither peaks nor troughs predicted success or failure; no patient with a trough <15µg/mL had a peak >40µg/mL	Troughs >15µg/mL associated with nephrotoxicity

Table I (continued)**: Summary of Studies, 1994 - 2005**

Study	Study population	Study design	Study type	Efficacy outcomes	Toxicity outcomes
Karam et al. (1997)	Patients receiving vancomycin for various infections (n=240)	Prospective; historic control	"Minimal" *vs.* traditional dosing approach	No difference in cure, improvement, failure, or time to eradication of infection; minimal approach cheaper	No difference in nephrotoxicity
Elting et al. (1998)	Oncology patients (n=742)	Prospective, consecutive	Observational toxicity study	Not assessed	Nephrotoxicity: 17%; risk factors: other nephrotoxins, Apache II >40; vancomycin concentrations not predictive
Pea et al. (2000)	ICU patients s/p cardiothoracic surgery (n=18)	Retrospective	Pharmacokinetic study	Concomitant drugs with hemodynamic effects may enhance vancomycin clearance by changing cardiac output, renal blood flow, or via other mechanisms	Not assessed
Wysocki et al. (2001)	Patients with various MRSA infections (n=119)	Prospective, randomized	Continuous *vs.* intermittent vancomycin infusion; serum concentration 20-25µg/mL	Clinical, microbiological outcomes not different; continuous infusion less expensive	No difference
Cohen et al. (2002)	Hospitalized patients (n=121)	Prospective, randomized	Daily *vs.* twice-daily vancomycin; mean peaks/troughs in the QD group: 42.8/16.1	No difference in clinical response	No difference in nephrotoxicity or ototoxicity (assessed by audiometry)
Darko et al. (2003)	Patients on a clinical pharmacology service, randomly selected (n=200)	Retrospective	Cost effectiveness study	Pharmacokinetic dose adjustment cost effective in ICU, oncology patients, and patients receiving concomitant nephrotoxins	Not assessed
Taber et al. (2003)	Adult liver transplant patients (n=20)	Retrospective	Pharmacokinetic study	Serum creatinine does not adequately predict GFR or vancomycin clearance	Not assessed
Iwamoto et al. (2003)	Patients with various MRSA infections (n=184)	Retrospective	Chart review	Shorter duration of therapy and less cumulative drug given in patients with peak concentrations >25	Less nephrotoxicity in the patients who received therapeutic drug monitoring (vancomycin concentrations in the non-TDM control group not measured)

ID Subcommittee Recommendations for Vancomycin Serum Level Monitoring

1. For patients in whom an accurate assessment of renal function is possible, vancomycin serum concentration monitoring is not necessary. Consult pharmacy for vancomycin dosing assistance.
2. Serum creatinine concentration should be measured at least weekly in all patients receiving vancomycin. More frequent monitoring of serum creatinine, e.g. twice weekly, is appropriate in patients receiving a concomitant aminoglycoside or another known nephrotoxic agent.
3. For patients in whom an accurate assessment of renal function is difficult, vancomycin serum concentration monitoring is reasonable. Appropriate candidates include:
   a) Patients with rapidly changing renal function
   b) Patients undergoing hemodialysis, especially with high flux dialysis membranes
   c) Patients undergoing continuous venovenous hemofiltration (CVVH)
   d) Obese patients
   e) Burn patients
4. For those patients in whom vancomycin serum concentration monitoring is reasonable, measurement of trough concentrations (i.e., immediately before infusing the next dose) is sufficient and weekly determinations are generally adequate. Although patients with renal failure may require more frequent monitoring, the practice of obtaining daily trough determinations is discouraged.
5. Although there are insufficient data at this time to recommend increasing the vancomycin trough range beyond 5–10µg/mL, the use of a higher range may be appropriate in certain clinical situations, such as osteomyelitis or endocarditis.

References

1. Bernard E, Perbost I, Carles M, Michiels A, Carsenti-Etesse H, Chichmanian RM, Dunais B, Dellamonica P. Efficacy and safety of vancomycin constant-rate infusion in the treatment of chronic Gram-positive bone and joint infections. Clin Microbiol Infect 3 (4): 440-446, 1997.
2. Cantu TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. Clin Infect Dis 18 (4): 533-43, 1994.
3. Cohen E, Dadashev A, Drucker M, Samra Z, Rubinstein E, Garty M. Once-daily versus twice-daily intravenous administration of vancomycin for infections in hospitalized patients. J Antimicrob Chemother 49 (1): 155-60, 2002.
4. Darko W, Medicis JJ, Smith A, Guharoy R, Lehmann DE. Mississippi mud no more: cost-effectiveness of pharmacokinetic dosage adjustment of vancomycin to prevent nephrotoxicity. Pharmacotherapy 23 (5): 643-50, 2003.
5. Elting LS, Rubenstein EB, Kurtin D, Rolston KV, Fangtang J, Martin CG, Raad, II, Whimbey EE, Manzullo E, Bodey GP. Mississippi mud in the 1990s: risks and outcomes of vancomycin-associated toxicity in general oncology practice. Cancer 83 (12): 2597-607, 1998.
6. Fernandez de Gatta MD, Calvo MV, Hernandez JM, Caballero D, San Miguel JF, Dominguez-Gil A. Cost-effectiveness analysis of serum vancomycin concentration monitoring in patients with hematologic malignancies. Clin Pharmacol Ther 60 (3): 332-40, 1996.
7. Geraci JE, Heilman FR, Nichols DR, Wellman WE. Antibiotic therapy of bacterial endocarditis. VII. Vancomycin for acute micrococcal endocarditis: preliminary report. Mayo Clin Proc 33: 172-81, 1958.
8. Iwamoto T, Kagawa Y, Kojima M. Clinical efficacy of therapeutic drug monitoring in patients receiving vancomycin. Biol Pharm Bull 26 (6): 876-9, 2003.
9. Karam CM, McKinnon PS, Neuhauser MM, Rybak MJ. Outcome assessment of minimizing vancomycin monitoring and dosing adjustments. Pharmacotherapy 19 (3): 257-66, 1999.
10. Kralovicova K, Spanik S, Halko J, Netriova J, Studena-Mrazova M, Novotny J, Grausova S, Koren P, Krupova I, Demitrovicova A, Kukuckova E, Krcmery V, Jr. Do vancomycin serum levels predict failures of vancomycin therapy or nephrotoxicity in cancer patients? J Chemother 9 (6): 420-6, 1997.
11. Kremery V, Jr., Netriova D, Studena M, Halko J. Monitoring vancomycin serum concentrations in cancer patients undergoing cytotoxic chemotherapy. Pediatr Infect Dis J 15 (2): 184, 1996.
12. Moellering RC, Jr., Krogstad DJ, Greenblatt DJ. Vancomycin therapy in patients with impaired renal function: a nomogram for dosage. Ann Intern Med 94 (3): 343-6, 1981.
13. Mulhern JG, Braden GL, O'Shea MH, Madden RL, Lipkowitz GS, Germain MJ. Trough serum vancomycin levels predict the relapse of gram-positive peritonitis in peritoneal dialysis patients. Am J Kidney Dis 25 (4): 611-5, 1995.
14. Pea F, Porreca L, Baraldo M, Furlanut M. High vancomycin dosage regimens required by intensive care unit patients cotreated with drugs to improve haemodynamics following cardiac surgical procedures. J Antimicrob Chemother 45 (3): 329-35, 2000.
15. Saunders NJ. Why monitor peak vancomycin concentrations? Lancet 344 (8939-8940): 1748-50, 1994.
16. Taber DJ, Fann AL, Malat G, Dupuis RE. Evaluation of estimated and measured creatinine clearances for predicting the pharmacokinetics of vancomycin in adult liver transplant recipients. Ther Drug Monit 25 (1): 67-72, 2003.
17. Welty TE, Copa AK. Impact of vancomycin therapeutic drug monitoring on patient care. Ann Pharmacother 28 (12): 1335-9, 1994.
18. Wysocki M, Delatour F, Faurisson F, Rauss A, Pean Y, Misset B, Thomas F, Timsit JF, Similowski T, Mentec H, Mier L, Dreyfuss D. Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother 45 (9): 2460-7, 2001.
19. Zimmermann AE, Katona BG, Plaisance KI. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. Pharmacotherapy 15 (1): 85-91, 1995.

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost‡	Therapeutic Classification	Use	Usual Adult Starting Dose*
Pemetrexed (Alimta)	Injection: 500mg	Folic acid antagonist	Malignant pleural mesothelioma; non-small cell lung cancer	500mg/m^2 IV on day 1 of each 21-day cycle
	Added as 1st line combination therapy (with cisplatin) for the treatment of malignant pleural mesothelioma and as a 2nd line agent for non-small cell lung cancer.			
Erlotinib (Tarceva)	Tablets: 25mg, 100mg, 150mg	Epidermal growth factor receptor inhibitor	Non-small cell lung cancer	150mg once daily.
Ropivacaine (Naropin)	Injection: 0.5% (20mL); 0.75% (20mL)	Amide local anesthetic	Surgical anesthesia	Smallest required for effect.
Meningococcal Vaccine (Menactra)	Injection: 4mcg each of groups A, C, Y, and W-135	Vaccine	Vaccination of 11-12 year old adolescents and for persons who have not been vaccinated previously before high-school entry (at ~ age 15 years).	0.5mL IM, preferably in the deltoid region.
	Note: Routine vaccination also is indicated for 1st-year college students living in dormitories and for other persons at increased risk (military recruits, travelers to areas in which meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of N. meningitidis, patients with anatomic or functional asplenia, and patients with terminal complement deficiency). Avoiding vaccinating persons who are not at high risk for meningococcal disease and who are known to have experienced GBS previously is prudent.			

Formulary Deletions	Dosage Form/Strength	Classification	Comment
Levobupivacaine	All forms and strengths	Amide local anesthetic	No longer available.
Thioridazine (Mellaril)	All forms and strengths	Antipsychotic agent	Low use item.

Other Actions

The UW Medicine *Vancomycin Serum Level Monitoring Guidelines* were approved (see lead story).

The *UWMC Adult Heparin Protocol Orders* were approved (see e-Drug Formulary under heparin; http://www.formchecker.com/FormChecker/servlet/FormSearch?txtype=search&reqfrom=quick&srchterm=heparin&search=Go).

* Refer to product labeling for full prescribing information. ‡ Contact pharmacy for information on drug costs.

Vol. 34, No. 12

UNIVERSITY OF WASHINGTON

DRUG INFORMATION CENTER
Box 354735
Seattle, WA 98195-4735

drug therapy topics