Sources for Antibiotic Pharmacokinetics Data & Equations

Ronald A. Herman, Ph.D.

Vancomycin Basic Pharmacokinetics

Liberation and Absorption - negligible

Distribution - (*Chapter 15, pp 330* - Burton ME, Shaw LM, Schentag JJ, Evans WE. *Applied Pharmocokinetics: Principles of Therapeutic Drug Monitoring.* 4th ed. Baltimore, MD: Lippincott, Williams & Wilkins; 2006.)

Measurable

Protein Binding 30-55%

Tissue Penetration - good

Lipid Solubility – Yes, but does not penetrate into normal CSF

Vancomycin Metabolism - Negligible

Kirby and Divelbiss, *Antibiot Ann* 1957,107-117.

Vancomycin Elimination and Distribution

Volume of Distribution $V_c = 0.15$ L/Kg
$V_{ss} = 0.5 – 0.9$ L/Kg

Elimination Half-lives

Alpha = 7 minutes Beta = 0.4 hours Gamma = 3-9 hours

Matzke GR, Zhanel GG and Guay DRP: Clinical pharmacokinetics of vancomycin. *Clin Pharmacokinet* 1986; 11:275-282

How do we measure it?

FPI – Florescence Polarization Immunoassay or EMIT® – Enzyme Multiplied Immunoassay

When do we do it? - *(Chapter 15, pp 336)*

When we reach steady state – 5 half-lives ~ around the fourth dose.

When distribution is complete – about one hour after the infusion stops.

Optimum sampling times.

Trough within 30 minutes of a scheduled dose.

Dose ≤ 1.25 g infuse over 90 minutes.

Dose 1.5 - 2 g infuse over 120 minutes.

Peak 60 minutes after the infusion stops.

Predicting Steady Levels

Target Concentrations

Peak	30-40 mg/L
Trough	10-20 mg/L

Prospectively (Population Pharmacokinetic Estimates)

$$\text{CrCl}\,(\text{ml/min}) = \frac{(140\text{-Age})\cdot CrClWt}{72\cdot SrCr}\cdot(0.85+Sex\cdot 0.15)$$ where *Sex* = 1 for a male and 0 for a female.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16(1):31-41.

Modified $\text{CrCl}\,(\text{ml/min}) = \frac{(140\text{-Age})\cdot CrClWt}{73\cdot(SrCr+0.07)}\cdot(0.85+Sex\cdot 0.15)$ where *Sex*=1 for a male and 0 for a female.

IBW (males)

50 Kg + 2.3 Kg/inch over 5 feet

IBW (females)

45.5 Kg + 2.3 Kg/inch over 5 feet

BMI = Wt (Kg) / (Ht (In) * 0.0254)^2

CorrSrCr = (SrCr + 0.07) / 0.987

Ann Pharmacother 2011;45:748-56.

If BMI is > 25 Kg/m^2, then **CrClWt** = IBW + 0.4*(ActBW – IBW)

If ActBW > IBW and BMI ≤ 25 **CrClWt** = IBW

If ActBW < IBW, then **CrClWt** = ActBW

$$Est\ k_e = \frac{8.3\cdot CrCl+44}{10000} \qquad Est\ V_{ss} = 0.7\ L/Kg\cdot ActBW$$

Matzke GR, McGory RW, Haslseneson CE and William FK: Pharmacokinetics of vancomycin with various degrees of renal function. Antimicrob Agents Chemother 1984; 25:433-437

TR Only: $\left(\text{Dose}/\text{Tau}\right)_{\text{new}} = \left(\text{Dose}/\text{Tau}\right)_{\text{current}} * \text{C}_{\text{desired}}/\text{C}_{\text{measured}}$ [$C_{desired}$ = Target 15 mg/L]

Retrospectively (Sawchuk - Zaske Approach to Dosage Adjustment) - Sawchuk RJ and Zaske DE: Pharmacokinetics of dosage regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J Pharmacokin Biopharm* 1976; 4:183-195.

1. Calculate the elimination rate constant.

$$k_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{\ln C_{pk} - \ln C_{tr}}{t_{tr} - t_{pk}} = \frac{\ln\left(C_{pk}/C_{tr}\right)}{\tau - t_{inf} - t_{pi}}$$

2. Calculate C_0 (t_{pk} = elapsed time from start of infusion)

$$C_0 = \frac{C_{pk}}{e^{-k_e\,(t_{pk}\,-\,t_{\text{inf}})}}$$

3. Calculate the half-life.

$$t_{1/2} = \frac{\ln 2}{k_e}$$

4. Calculate the volume of distribution.

$$V_{ss} = \frac{R_0}{k_e}\cdot\frac{1-e^{-k_e t_{\text{inf}}}}{(C_0 - C_{tr}\cdot e^{-k_e t_{\text{inf}}})}$$

5. Calculate the dosing interval.

$$\tau = \frac{\ln\left(C_{Max,desired}/C_{Min,desired}\right)}{k_e} + t_{\text{inf}}$$

6. Calculate the new infusion rate.

$$\boldsymbol{R_0 = C_{Max,desired}\cdot k_e\cdot V_{ss}\cdot\frac{\left(1-e^{-k_e\tau}\right)}{\left(1-e^{-k_e t_{\text{inf}}}\right)}}$$

7. Calculate the new peak.

$$C_{ss,pk} = \frac{R_0}{V_{ss}\cdot k_e}\cdot\frac{\left(1-e^{-k_e t_{\text{inf}}}\right)}{\left(1-e^{-k_e\tau}\right)}$$

8. Calculate the new trough.

$$C_{ss,tr} = C_{ss,pk}\cdot e^{-k_e\left(\tau - t_{\text{inf}}\right)}$$

Aminoglycoside Basic Pharmacokinetics

Liberation and Absorption - *Peak following IM administrations is 30-120 minutes after administration. Oral 0.3-15% of the oral dose is absorbed.*

Distribution - *(Chapter 14, pp 287)*

Measurable

Protein Binding < 10%

Tissue Penetration - *Distributes well in body fluids; synovial, peritoneal, ascitic and pleural.*

Lipid Solubility - *Poor: Does not penetrate into adipose tissue or normal CSF.*

Metabolism - *Only 5-15%* Gyselynck et al, *J Infect Dis* 1971,S70-6.

Elimination and Distribution - *(Chapter 14, pp 289-292)*

Volume of Distribution (V_{ss})

Normal = 0.2-0.25 L/Kg
Dehydrated = 0.15 L/Kg and Overhydrated = 0.3 L/Kg

Elimination Half-lives

Alpha = 5 minutes Beta = 2-4 hours Gamma = 100 hours

Pharmacodynamic Characteristics: (*Chapter 16, pp 342-347*)

Concentration Effect Relationships.

Concentration Dependent Activity (Peak:MIC ratio or AUC:MIC ratio)
Activity is associated with high ratios.

Post-antibiotic Effect (PAE) – *The persistent inhibitory effect of the antibiotic following its removal*.

Toxicity Considerations: (*Chapter 14, pp 293-298*)

Nephrotoxicity:

- Generally reversible
- Thought to be due to prolonged trough elevation > 2 mg/L

Ototoxicity:

- Often not reversible
- May be due to elevated peaks, but data unclear

Two Dosing Approaches

Traditional (Multiple Dosing) Approach: (*Chapter 14, p 306*)

Dose to achieve a target peak and trough concentration.

	Peak (mg/L)	Trough (mg/L)	Peak (Life Threatening infection)	Peak (Serious Infection)	Peak (Synergy/UTI)
Gentamicin	6-10	1	8-10 mg/L	6-8 mg/L	4-6 mg/L
Tobramycin	6-10	1	8-10 mg/L	6-8 mg/L	4-6 mg/L
Amikacin	20-30	10	25-30 mg/L	20-25 mg/L	15-20 mg/L

Dosing intervals generally range from every 8 (*good renal function*) to 24 hours (*poor renal function*).

Extended Interval (Once Daily) Approach (*Chapter 14, pp 304-305*)

Dose to optimize the peak:MIC ratio

Approximately 10:1 to 20:1

Dosing interval is usually every 24 hours

Thought to reduce toxicity

Multiple Dosing Regimen Concentrations

When we reach steady state: 5 half-lives ~ around the third dose.

When distribution is complete: 30 minutes after the infusion is complete.

Length of infusion: 30 minutes

Optimum sampling times:

Trough within 30 minutes of a scheduled dose.

Peak 30 minutes after the infusion stops.

Extended Interval Regimen Concentration

Infusion length: 60 minutes.

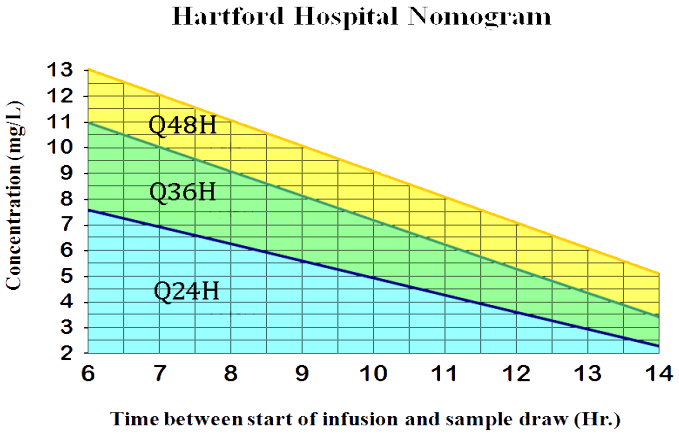
Sampling time: Collect a single sample 6-14 hours after the initial dose.

Extended Interval Dosing (Nicolau: *Antimicrob Agents Chemother* 1995)

Initial Dose (Adults): 5-7 mg/Kg

Initial Dosing and Interval (Adults):

Cl_{cr} > 60 ml/min	7 mg/Kg every 24 hours
Cl_{cr} 40 to 60 ml/min	7 mg/Kg every 36 hours
Cl_{cr} 20 to 40 ml/min	7 mg/Kg every 48 hours
Cl_{cr} < 20 ml/min	Conventional dosing should be used.



Initial Dosing and Interval (Pediatrics):

3 mo. – 2 years	9.5 mg/Kg every 24 hours
2 – 8 years	8.5 mg/Kg every 24 hours
> 8 years	7.0 mg/Kg every 24 hours

McDade EJ, Wagner JL, Moffett BS, Palazzi DL. Once-daily gentamicin dosing in pediatric patients without cystic fibrosis. *Pharmacotherapy* 2010;30(3):248-53.

Dosage Adjustment:

According to the nomogram.

Selected References

1. Andres I, Lopez R, Pou L, Pinol F, Pascual C. Vancomycin Monitoring: One Or Two Serum Levels? *Ther Drug Monit* 1997; **19**(6):614-619. **(IDIS Article 398718)**
2. Asbury WH, Darsey EH, Rose WB, Murphy JE, Burrington DE, Capers CC: Vancomycin pharmacokinetics in neonates and infants: a retrospective evaluation. *Ann Pharmacother* 1993;**27**:490-6.
3. Begg EJ, Barclay ML. Aminoglycosides--50 Years on. *Br J Pharmacol* 1995; **39**(6):597-603. **(IDIS Article 350380)**
4. Begg EJ, Barclay ML, Duffull SB. A Suggested Approach to Once-Daily Aminoglycoside Dosing. *Br J Clin Pharmacol* ; 1995; **39**(6):605-609. **(IDIS Article 350381)**
5. Begg EJ, Barclay ML, Kirkpatrick CMJ. The Therapeutic Monitoring of Antimicrobial Agents. *Br J Pharmacol* 2001; **52**(S1):35S-43S. **(IDIS Article 469267)**
6. Benkert SC, Sinnett MJ, Amodio-Groton M. Impact of Monitoring Vancomycin Peak and Trough Concentrations Versus Trough Concentrations Alone on Dose Adjustments: An Outcomes Analysis. *J Pharm Technology;* 2000; **16**(6):236-240. **(IDIS Article 456683)**
7. Cantu TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. *Clin Infect Dis* 1994; **18**(4):533-543. **(IDIS Article 328671)**
8. De Broe ME, Paulus GJ, Verpooten GA, Roels F, Buyssens N, Wedeen R et al. Early effects of gentamicin, tobramycin, and amikacin on the human kidney. *Kidney Int* 1984; **25**(4):643-652.
9. Dipiro JT, Edmiston CE, Bohnen JM. Pharmacodynamics of antimicrobial therapy in surgery. [Review] [46 refs]. *Am J Surg* 1996; **171(6):**615-22. **(IDIS Article 370003)**
10. Ducharme MP, Slaughter RL, Edwards DJ. Vancomycin pharmacokinetics in a patient population: effect of age, gender, and body weight. *Ther Drug Monit* 1994; **16**(5):513-518. **(IDIS Article 335790)**
11. Freeman CD, Quintiliani R, Nightingale CH. Vancomycin therapeutic drug monitoring: is it necessary? *Ann Pharmacother* 1993; **27**(5):594-598. **(IDIS Article 314178)**
12. Golper TA, Noonan HM, Elzinga L, et al: Vancomycin pharmacokinetics, renal handling and nonrenal clearances in normal human subjects. *Clin Pharmacol Ther* 1988;**43**:565-570.
13. Hammett-Stabler CA, Johns T. Laboratory Guidelines for Monitoring of Antimicrobial Drugs. *Clin Chem* ; 1998; **44**(5):1129-1140. **(IDIS Article 408041)**
14. Healy DP, Polk RE, Garson ML, Rock DT, Comstock TJ. Comparison of steady-state pharmacokinetics of two dosage regimens of vancomycin in normal volunteers. *Antimicrob Agents Chemother* 1987; **31**(3):393-397. **(IDIS Article 227072)**
15. Healy DP, Sahai J, V, Fuller SH, Polk RE. Vancomycin-Induced Histamine Release and "Red Man Syndrome": Comparison of 1- and 2-Hour Infusions. *Antimicrob Agts Chemother ;* 1990; **34**(4):550-554. **(IDIS Article 264897)**
16. Karam CM, Mckinnon PS, Neuhauser MM, Rybak MJ. Outcome Assessment of Minimizing Vancomycin Monitoring and Dosing Adjustments. *Pharmacotherapy* 1999; **19**(3):257-266. **(IDIS Article 422544)**
17. Leader WG, Chandler MH, Castiglia M: Pharmacokinetic optimisation of vancomycin therapy. [Review*] Clin Pharmacokinet* 1995;**28:**327-42.
18. Macgowan AP, Reeves DS. Serum monitoring and practicalities of once-daily aminoglycoside dosing. *J Antimicrob Chemother* 1994; **33**(2):349-350. **(IDIS Article 326509)**
19. Marra F, Partovi N, Jewesson P. Aminoglycoside administration as a single daily dose. An improvement to current practice or a repeat of previous errors? *Drugs* 1996; **52**(3):344-370.

20. Matzke GR, McGary RW, Halstenson CE, Keane WI: Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1984;**25**:433-437.
21. Matzke GR, Zhanel GG, Guay DRP: Clinical pharmacokinetics of vancomycin. *Clin Pharmacokinet* 1986;**11**:257-282.
22. McDonald PJ, Wetherall BL, Pruul H. Postantibiotic leukocyte enhancement: increased susceptibility of bacteria pretreated with antibiotics to activity of leukocytes. *Rev Infect Dis* 1981; **3(1)**:38-44.
23. Moellering RC Jr.: Pharmacokinetics of vancomycin. [Review] *J Antimicrob Chemother* 1984;**14 Suppl D**:43-52.
24. Moellering RC, Jr., Krogstad DJ, Greenblatt DJ. Pharmacokinetics of vancomycin in normal subjects and in patients with reduced renal function. *Rev Infect Dis* 1981; **3 suppl**:S230-S235. **(IDIS Article 167575)**
25. Mondorf AW, Breier J, Hendus J, Scherberich JE, Mackenrodt G, Shah PM et al. Effect of aminoglycosides on proximal tubular membranes of the human kidney. *Eur J Clin Pharmacol* 1978; **13**(2):133-142. **(IDIS Article 104662)**
26. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis* 1987; **155**(1):93-9. **(IDIS Article 223589)**
27. Moore RD, Smith CR, Lietman PS. Risk factors for the development of auditory toxicity in patients receiving aminoglycosides. *J Infect Dis* 1984; **149**(1):23-30. **(IDIS Article 181979)**
28. Mulhern JG, Braden GL, O'Shea MH, Madden RL, Et AL. Trough Serum Vancomycin Levels Predict the Relapse of Gram-Positive Peritonitis in Peritoneal Dialysis Patients. *Am J Kidney Dis* 1995; **25**(4):611-615. **(IDIS Article 345389)**
29. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother* 1995; **39(**3):650-655. **(IDIS Article 343925)**
30. Nicolau DP, Wu AH, Finocchiaro S, Udeh E, Chow MS, Quintiliani R et al. Once-daily aminoglycoside dosing: impact on requests and costs for therapeutic drug monitoring. *Ther Drug Monit* 1996; **18**(3):263-266. **(IDIS Article 368021)**
31. Ohtani I, Ohtsuki K, Aikawa T, Omata T, Ouchi J, Saito T. Ototoxicity of aminoglycoside antibiotics by rapid intravenous injection. ORL *J Otorhinolaryngol Relat Spec* 1982; **44**(3):156-169.
32. Pauly DJ, Musa DM, Lestico MR, Lindstrom MJ, Hetscko CM,: Risk of nephrotoxicity with combination vancomycin-aminoglycoside antibiotic therapy. *Pharmacotherapy* 1990;**10:**378-82.
33. Periti P. Pharmacoeconomic evaluation of once-daily aminoglycoside treatment. *J Chemother* 1995; **7**(4):380-394.
34. Polk RE, Healy DP, Schwartz LB, Rock DT, Et AL. Vancomycin and the Red-Man Syndrome: Pharmacodynamics of Histamine Release. *J Infect Dis ;* 1988; **157**(3):502-507. **(IDIS Article 239516)**
35. Pou L, Rosell M, Lopez R, Pascual C. Changes in Vancomycin Pharmacokinetics During Treatment. *Ther Drug Monit* 1996; **18**(2):149-153. **(IDIS Article 362617)**
36. Pryka RD. Vancomycin serum concentration monitoring: a continued debate. *Ann Pharmacother* 1994; **28**(12):1397-1399. **(IDIS Article 340460)**

37. Rodman DP, Maxwell AJ, McKnight JT. Extended dosage intervals for aminoglycosides. [Review] [50 refs]. *Am J Hosp Pharm* 1994; **51**(16):2016-21. **(IDIS Article 333914)**
38. Rodvold KA, Blum RA, Fischer JH, Zokufa HZ, Rotscafer JC, Crossley KB, Riff LJ: Vancomycin pharmacokinetics in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1988;**32:**848-52.
39. Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH: Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother* 1990;**25**:679-687.
40. Sawchuk RJ, Zaske DE: Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: Gentamicin in burn patients. *J Pharmacokin Biopharm* 1976;**4**:183-195.
41. Schaad UB, McCracken GH, Nelson JD: Clinical pharmacology and efficacy of vancomycin in pediatric patients. *J Pediatr* 1980;**96**:119-126.
42. Sorrell TC, Packham DR, Shanker S, Foldes M, Munro R: Vancomycin therapy for methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982;**97**:344-350.
43. Streetman DS, Nafziger AN, Destache CJ, Bertino AS, Jr. Individualized pharmacokinetic monitoring results in less aminoglycoside-associated nephrotoxicity and fewer associated costs. *Pharmacotherapy* 2001; **21**(4):443-451. **(IDIS Article 468898)**
44. Van Lent-Evers NAE, Mathot RAA, Geus WP, Van Hout BA, Vinks AAT. Impact of Goal-Oriented and Model-Based Clinical Pharmacokinetic Dosing of Aminoglycosides on Clinical Outcome: A Cost-Effectiveness Analysis. *Ther Drug Monit* ; 1999; **21**(1):63-73. **(IDIS Article 420768)**
45. Vogelman B, Craig WA. Kinetics of antimicrobial activity. *J Pediatr* 1986; **108**(5 Pt 2):835-40. **(IDIS Article 216824)**
46. Vogelman B, Gudmundsson S, Turnidge J, Leggett J, Craig WA. In vivo postantibiotic effect in a thigh infection in neutropenic mice. *J Infect Dis* 1988; **157**(2):287-98.
47. Wallace MR, Mascola JR, Oldfield EC. Red Man Syndrome: Incidence, Etiology, and Prophylaxis. *J Infect Dis ;* 1991; **164**(6):1180-1185. **(IDIS Article 294459)**
48. Welty TE, Copa AK. Impact of Vancomycin Therapeutic Drug Monitoring on Patient Care. *Ann Pharmacother* 1994; **28**(12):1335-1339. **(IDIS Article 340449)**
49. Zaske DE, Cipolle RJ, Rotschafer JC, Solem LD, Mosier NR, Strate RG. Gentamicin pharmacokinetics in 1,640 patients: method for control of serum concentrations. *Antimicrob Agents Chemother* 1982; **21**(3):407-11. **(IDIS Article 146363)**
50. Zimmermann AE, Katona BG, Plaisance K, I. Association of Vancomycin Serum Concentrations with Outcomes in Patients with Gram-Positive Bacteremia. *Pharmacotherapy* 1995; **15**(1):85-91. **(IDIS Article 341190)**