Aminoglycoside dosing

I. Introduction

The aminoglycosides are the mainstay in the treatment of serious gram-negative systemic infections. A disadvantage of the aminoglycosides is their association with nephrotoxicity and ototoxicity, both of which are associated with elevated trough levels and sustained elevated peak levels.

1. Antimicrobial spectrum

   Aminoglycosides have bactericidal activity against most gram-negative bacteria including *Acinetobacter, Citrobacter, Enterobacter, E. Coli, Klebsiella, Proteus, Providencia, Pseudomanas, Salmonella, Serratia* and *Shigella*. The MIC's of gram negative bacteria are usually less than 2 mcg/ml for gentamicin and tobramycin and 8 mcg/ml for amikacin.

   Aminoglycosides are active against most strains of *Staphylococcus aureus* and *S. epidermidis*. Most strains of enterococcus are resistant to aminoglycosides alone, however when used in combination with penicillins they are often effective in enterococcal endocarditis due to synergistic antimicrobial mechanisms. Anaerobic bacteria are universally resistant because aminoglycoside transport into cells is oxygen-dependent.

2. Toxicity

   Aminoglycoside nephrotoxicity manifests clinically as nonoliguric renal failure, with a slow rise in serum creatinine and a hypoosmolar urinary output developing after several days of therapy. The reported incidence of nephrotoxicity varies substantially between studies, averaging 6% to 10%. Nephrotoxicity rates do not vary significantly among the different aminoglycosides. Factors associated with nephrotoxicity include duration of treatment, increasing age, compromised renal function, volume depletion, elevated peak and trough levels, concurrent nephrotoxic drugs (i.e., vancomycin) and previous exposure to aminoglycosides.

   Aminoglycosides can cause **permanent** vestibular and/or auditory ototoxicity. Overt otoxicity occurs in 2% to 10% of patients treated with aminoglycosides. Factors associated with otoxicity include increasing age, duration of therapy, elevated peak and trough levels, concurrent loop diuretics or vancomycin, underlying disease states and previous exposure to aminoglycosides.

   Vestibulotoxicity is difficult to diagnose and there is no reliable monitoring process. Recent studies indicate a genetic predisposition to aminoglycoside auditory ototoxicity due to a mutation of mitochondrial DNA.[23,24] However, this genetic component does not appear to influence aminoglycoside vestibular ototoxicity. Gentamicin toxicity is the most common single known cause of bilateral vestibulopathy, accounting for 15-50% of all cases.[25] A web site, Wobblers Anonymous presents personal testimony from patients who have suffered from this disabling ADE.

3. Concentration-toxicity relationships

   For gentamicin, tobramycin and netilmicin, the risk of ototoxicity and nephrotoxicity is

increased if peak levels are consistently maintained above 12 to 14 mcg/ml or trough levels consistently exceed 2 mcg/ml. For amikacin, peak levels above 32 to 34 mcg/ml or trough levels greater than 10 mcg/ml have been associated with a higher risk of ototoxicity and nephrotoxicity.

4. Concentration-efficacy relationships

   The pharmacodynamic properties of aminoglycosides are:

   - Concentration-**dependent** killing
   - **Significant** post-antibiotic effect

   Aminoglycosides eliminate bacteria quickest when their concentration is appreciably above the MIC for an organism, this is referred to as concentration dependent activity. The aminoglycosides also exhibit a significant post-antibiotic effect (PAE). PAE is the persistent suppression of bacterial growth following antibiotic exposure. Practically speaking this means that trough levels can drop below the MIC of targeted bacteria for a sustained period without decreasing efficacy.

   For AG's the ideal dosing regimen would **maximize concentration**, because the higher the concentration, the more extensive and the faster is the degree of bacteriocide. Therefore, the Peak/MIC ratio is an important predictor of efficacy. It has been shown that aminoglycosides eradicate bacteria best when they achieve a Peak/MIC ratio of at least 8-10. Therefore it is important to give a large enough dose to produce a peak level 8 to 10 times greater than the MIC.

   Aminoglycoside Pharmacodynamics in Vivo

Initial serum peak level	Died	Survived
< 5mcg/ml	**21%**	**79%**
>= 5mcg/ml	**2%**	**98%**

   Moore et al, J Infect Dis 149: 443, 1984

5. Pharmacokinetic parameters

   When given by IV infusion over 30 minutes, aminoglycosides follow a 3-compartment pharmacokinetic model; alpha (distribution), ß (elimination), and gamma (tissue release). When infused over one hour, the distribution phase is usually not observed. The gamma phase begins approximately sixteen hours post infusion, drug that was tissue bound to various organs is released. The amount released from tissue is very small, but does accumulate over time, contributing to AG toxicity.

   Although this model accurately represents the time course of AG serum levels, it cannot be used clinically because of its complexity. Therefore, the simpler one compartment model is widely used, and does, in fact, accurately predict serum AG levels.

   Volume of distribution
   The average Vd of AG's in otherwise healthy adults is 0.26 L/kg (range: 0.2-0.3). Although AG's do not distribute into adipose tissue, they do enter the extracellular fluid contained therein. Therefore, obese patients require a correction in the weight used for Vd calculation: LBW + 40% of weight above LBW. Patients with cystic fibrosis have a markedly increased Vd of 0.35

L/kg due to increases in extracellular fluid brought about by the disease process. Patients with ascites have additional extracellular fluid because of accumulation of ascitic fluid, which increases the Vd to approximately 0.32 L/kg. ICU patients may have a Vd 25-50% above normal.

Elimination rate
AG elimination is closely correlated with creatinine clearance, the average value for the slope is between 0.0024 and 0.0029 and the y-intercept is typically 0.01 to 0.015. Cystic fibrosis patients show a 50% increase in elimination rate. A major body burn increases the basal metabolic rate resulting in a marked increase in AG elimination. ICU patients are often hyper metabolic and therefore eliminate AG's more rapidly.

6. Dosing methods

Achieving therapeutic serum levels of aminoglycosides early in the course of treatment is critical to therapeutic success. Dosing error on the high side is preferable to the risks of under-treatment. An adequate loading dose is critical for rapid attainment of therapeutic peak levels.

The method of Sarrubi and Hull[4] utilizes serum creatinine, lean body weight, age, and sex to estimate creatinine clearance. This method considers more patient variables, which may improve the estimation of aminoglycoside elimination. Lesar et al found that the Sarubbi and Hull nomogram achieved therapeutic concentrations in 78% of patients.[9] Tsubaki and Chandler evaluated 5 methods for determining initial dosing requirements for gentamicin. They concluded that the Sarubbi and Hull method was the most accurate.[22] However, dosing nomograms are initial guidelines only. They can produce substantial variations in serum concentrations and should be subsequently adjusted based on serum level determinations and clinical response.

Dosage regimens necessary to achieve therapeutic aminoglycoside serum concentrations can be quantitatively determined by using simple pharmacokinetic principles. Individualized pharmacokinetic parameters are determined from the patient's serum concentration versus time data. Sawchuk and Zaske have described a method for establishing multiple infusion regimens based on individually calculated pharmacokinetic parameters.[3] Lesar, et al found that this individualized method achieved therapeutic concentrations in 90% of patients.[9]

For evaluation of serum level data, methods incorporating Bayesian principles appear to give the best overall predictive performance compared with traditional methods of vancomycin dosage adjustment. The Bayesian approach combines both population and patient-specific information (i.e., serum level data) in predicting dosage requirements.

Extended-interval aminoglycoside dosing has gained popularity in recent years. This simplified dosing method is appropriate in young, otherwise healthy patients with sepsis. However, there are many patient groups who are not candidates for this dosing methodology: the elderly, CrCl less than 30, dialysis, pregnancy, endocarditis, cystic fibrosis, ascites, neutropenia, infants, 20% or greater BSA burns, history of hearing loss or vestibular dysfunction, gram positive infections (when aminoglycoside is used for synergy), or mycobacterial infections.

II. Monitoring parameters

1. The following patient parameters should be monitored during aminoglycoside therapy:

a. Aminoglycoside peak and trough levels
   Obtain levels 24 hours after initiating therapy, at steady state (approximately four half-lives), and every 2 to 3 days.
b. BUN and serum creatinine
   Measure every two days, or every day in unstable renal function.
c. Weight
   Weigh patient every two to seven days.
d. Urine output
   Measure and monitor urine output daily
e. Baseline and weekly audiograms, and check for tinnitus or vertigo daily.

2. Therapeutic serum concentrations (mcg/ml)
   a. Gent/Tobra/Netilmicin Amikacin/Kanamycin
      Peak
      Serious infection: 6-8
      Life-Threatening infection: 8-10
      Trough
      Serious infection: 0.5-1.5
      Life-Threatening infection: 1- <2

   b. Amikacin/Kanamycin
      Peak
      Serious infection: 20-25
      Life-Threatening infection: 25-30
      Trough
      Serious infection: 1-4
      Life-Threatening infection: 4-8

III. Precautions

1. Proper timing of serum sampling is critical.

   The trough sample should be obtained 30 minutes prior to the dose. Measure the peak level 15 to 30 minutes after completion of the IV infusion to avoid the distributive phase. Measure the peak level 90 minutes after an IM injection. Drawing the peak too soon will result in inaccurate analysis.

   Drawing at exactly the right time is not as important as having the lab note the **exact times** that the samples were drawn. Also, have the nurse note the **exact times** that the sample infusion was started and when it ended. Please be aware of the widespread policy of nursing personnel to record a dose as having been given exactly as ordered if it is given within 30 minutes of the recorded time. This will lead to significant errors in analysis, have everyone record the **exact times**.

   This issue cannot be stressed enough. Inaccurate recording of drug administration times and lab draw times are the greatest source of calculation error, having a greater effect than pharmacy preparation error or lab assay error.

2. Outliers

   In general the Bayesian approach to the determination of individual drug-dosage requirements

performs better than other approaches. However, outlying patients in a population (ie, those patients whose pharmacokinetic parameters lie outside of the 95th percentile of the population) may be put at risk. As is always the case, the computerized algorithms outlined below can only assist in the decision-making process and should never become a substitute for rational thought or informed judgement.

IV. Program procedure

Before calculating an initial dose or analyzing serum level data, enter the target peak and trough levels and the standard length of infusion.

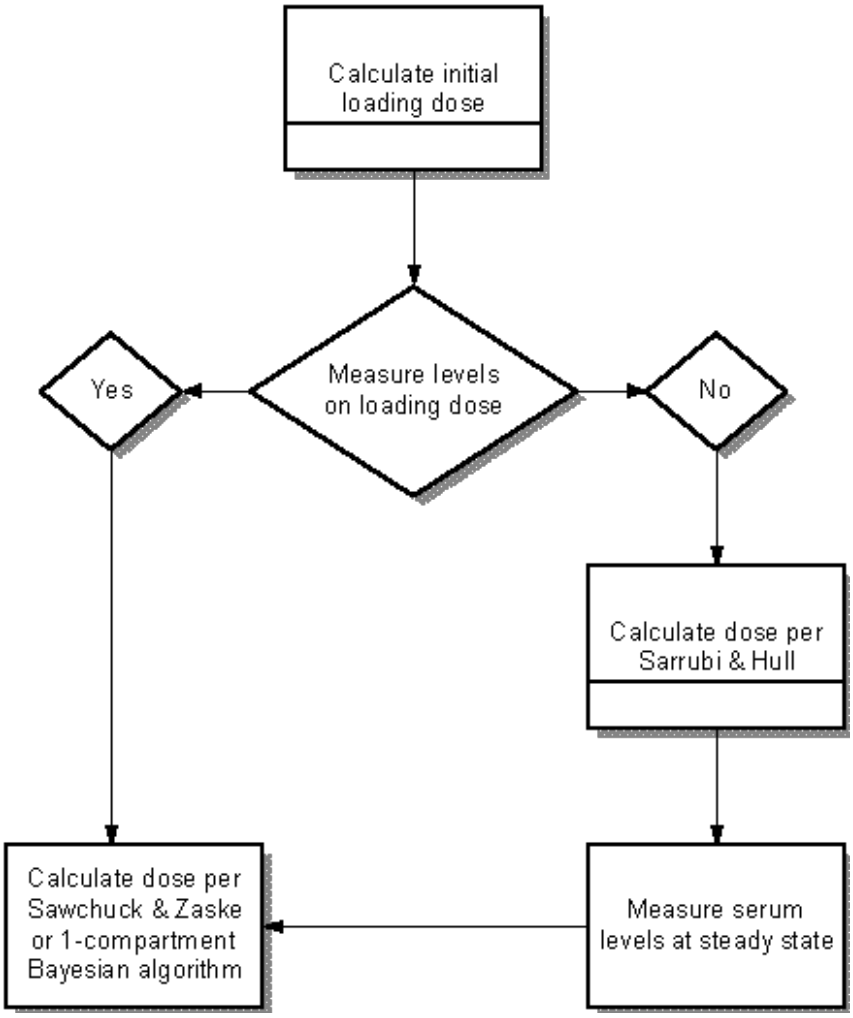
A. **Initial dosing**
The program calculates an ideal dose and interval, the user enters a practical dose and interval. The program then displays estimated steady-state peak and trough serum levels.

B. **Dosage adjustment based on serum levels**
Enter the current dosage regimen, date and time of sample infusion and date and time of serum level(s). The program calculates an ideal maintenance dose and the user enters a practical maintenance dose and interval. The program then displays estimated steady-state peak and trough serum levels.

The program supports six different serum level analysis methods for the one-compartment model:

Available one-compartment serum level analysis methods

V. Aminoglycoside dosing flow chart



VI. Pharmacokinetic formulas

The aminoglycoside model is not hard-coded into the program. The parameters are found in the drug model database and are fully user-editable. You can tailor each drug model to fit your patient population, or you can create your own models. See the Edit drug models section of the help file for further information.

A. Initial dosing

An initial dose, prior to serum level measurement, is based solely on the population model As stated above, the pk models supplied with the program may be edited, also multiple models of the same drug may be added to reflect different patient populations.

1. Determine dosing weight (DW)
   DW = LBW + ((ABW - LBW) x CF)
   where ABW = actual weight
   CF is a correction factor for obesity, **usually 40%**, but literature values vary:
   - Amikacin = 38%
   - Gentamicin = 43%
   - Kanamycin = no correction
   - Netilmicin = 50%
   - Tobramycin = 58%

2. Determine loading dose (LD)
   Gentamicin, Tobramycin, Netilmicin: LD = 2mg/kg DW
   Amikacin & Kanamycin: LD = 7.5mg/kg DW

3. Determine maintenance dose (MD)
   i. Estimate elimination rate (Kel)
      Kel = 0.01 + (CrCl x 0.0024)
   ii. Estimate Volume of distribution (Vd)
      Vd = 0.27 L/kg x DW
   iii. Calculate ideal maintenance dose (IMD)
      $IMD = Kel \times Vd \times Cptmax \times (1 - e^{-Kel \times tau} / 1 - e^{-Kel \times tinf})$
   iv. User selects practical dosage and interval
   v. Calculate expected peak & trough levels
      $Peak = (MD / t_{inf} \times Vd \times Kel) \times (1 - e^{-Kel \times tinf} / 1 - e^{-Kel \times tau})$
      $Trough = Peak * e^{-Kel \times (tau - tinf)}$
      where tinf = length of infusion

B. Adjusting maintenance dose using Sawchuk and Zaske's method

Patient specific pharmacokinetic parameters are calculated using the proven pharmacokinetic method of Sawchuk and Zaske.[3]

1. Determine elimination rate (Kel)
   Kel = (ln Cpmax/Cpmin') / time between samples
   where Cpmax = Peak level
   Cpmin'= Trough after dose

2. Determine Volume of distribution (Vd)
   $VD = [(Dose/tinf) / kel] \times (1- e^{-Kel \times tinf}) / Cpmax - (Cpmin \times e^{-Kel \times t'})$
   where Cpmax = Peak levelCpmin = Trough level before the dose
   t' = hours between time Cpmin drawn and end of infusion

3. Determine ideal dosing interval (tau)
   $tau = tinf + (-1 /Kel) \times \ln (Cptmax/Cptmin)$
   where Cptmin = Target trough
   Cptmax = Target peak

4. Determine ideal maintenance dose (IMD)
   $IMD = Kel \times Vd \times Cptmax \times (1 - e^{-Kel \times tau} / 1 - e^{-Kel \times tinf})$

5. User selects practical dosage and interval

6. Calculate expected peak & trough levels
   $CPssmax = (MD / t_{inf} \times Vd \times Kel) X (1 - e^{-Kel \times tinf} /1 - e^{-Kel \times tau})$
   $CPssmin = Peak * e^{-Kel \times (tau - tinf)}$

C. Adjusting maintenance dose using Bayesian 1-compartment model

1. Minimize Bayesian function

The Bayesian method uses population-derived pharmacokinetic parameters (ie., Vd and kel) as a starting point and then adjusts those parameters based on the serum level results, taking into consideration the variability of the population-derived parameters and the variability of the drug assay procedure. To achieve that end, the least squares method based on the Bayesian algorithm estimates the parameters which minimize the following function:[11]

$$SS = \sum_{i=1}^{n} (C_i - f(t_i, P))^2 / \sigma_i^2 + \sum_{j=1}^{m} (\bar{p}_j - p_j)^2 / \omega_j^2$$

where

n	number of data points
m	number of parameters
C	measured serum level
$f(t, P)$	predicted serum level from population model
σ	standard deviation of serum level data
$\bar{p}$	population parameter
p	estimated parameter
ω	standard deviation of population parameter

2. Determine ideal dosing interval (tau)
   Same as Sawchuk and Zaske's method

3. Determine ideal maintenance dose
   Same as Sawchuk and Zaske's method

4. User selects practical dosage and interval

5. Calculate expected peak & trough levels
   Same as Sawchuk and Zaske's method

D. Extended interval method - Initial dose

1. Determine dosing weight (DW)
   Same as Sawchuk and Zaske's method

2. Determine maintenance dose (MD)
   MD = DW x QDdose
   where QDdose is:
   - Amikacin, kanamycin = 15 mg/kg
   - Gentamicin, Tobramycin, Netilmicin = 5 mg/kg

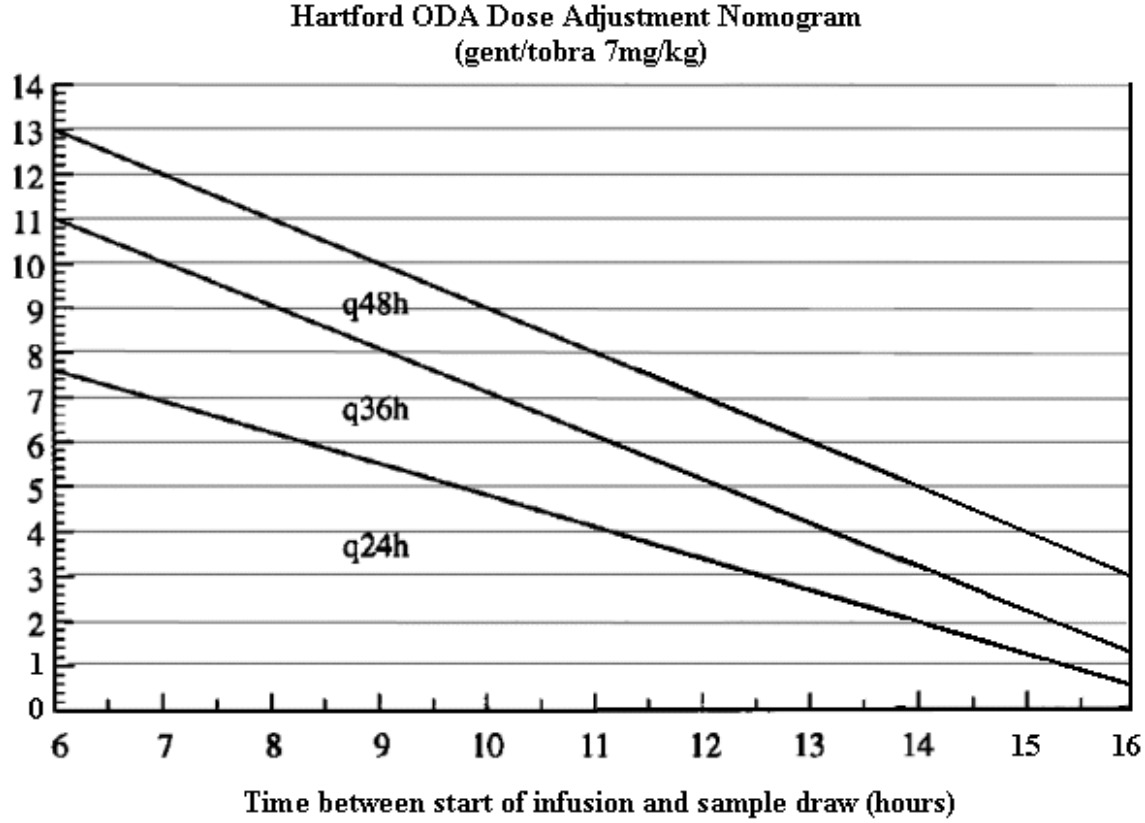
3. Determine interval
   The initial interval is based on estimated creatinine clearance:

CrCl	Interval
60 and above	24 hours
40 to 59	36 hours
30 to 39	48 hours
Less than 30	Use traditional dosing method

E. Extended interval method - Adjust maintenance dose

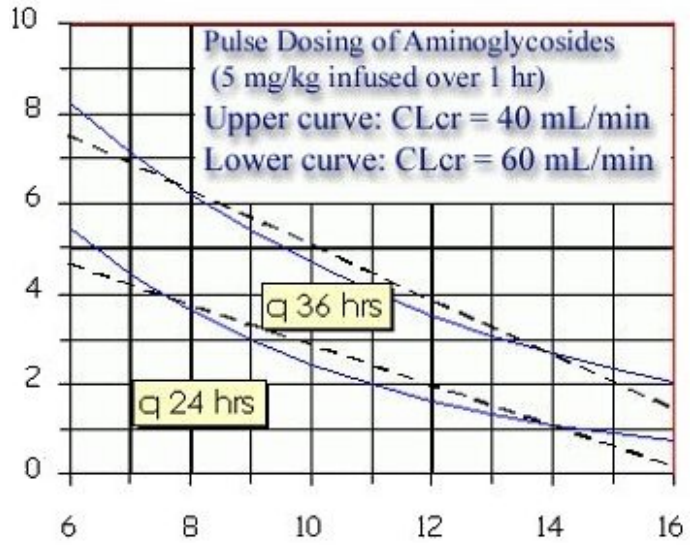
1. Determine interval
   Obtain a mid-interval drug level 6 to 16 hours after the initial dose, then evaluate the level using the interval adjustment nomogram. If the 6 to 16 hour level is undetectable and the infection is not responding, consider changing to a traditional dosing method.

   The three interval break points on the Hartford interval adjustment nomogram (illustrated below) are the approximate decay curves from a 7mg/kg gentamicin dose. These decay curves were calculated using a one compartment model with a volume of distribution of 0.25 L/kg and an elimination rate calculated from creatinine clearances of 25, 40, and 60 ml/min for 48, 36, and 24 hour intervals respectively. The authors of the Hartford nomogram then flattened these decay curves to simplify the nomogram. To use the Hartford nomogram for 15mg/kg doses of amikacin, multiply the drug-level scale by a factor of two. [5]



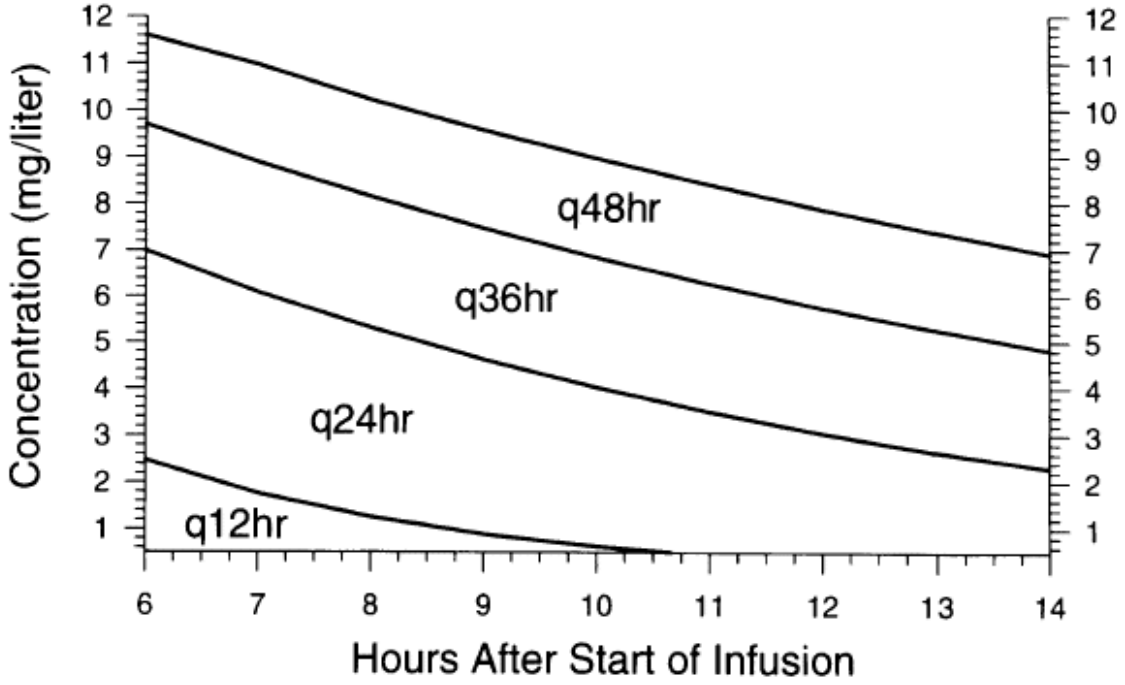
   It is important to note that the Hartford interval adjustment nomogram is only valid for a 7mg/kg dose. A nomogram for the less aggressive dose of 5mg/kg was developed by a consensus panel (illustrated below). The consensus panel argues that the 48 hour interval should be abandoned and that patients with a CrCl less than 40ml/min should be dosed by traditional pharmacokinetic methods. To use the consensus nomogram for 15mg/kg doses of amikacin, multiply the drug-level scale by a factor of three. [20]

Consensus ODA dose adjustment nomogram



The consensus panel also suggests that younger patients with excellent renal function may require Q 12 hour dosing. A 5mg/kg dosing algorithm for this subpopulation has been proposed by Urban and Craig (illustrated below). To use the Urban and Craig nomogram for 15mg/kg doses of amikacin, multiply the drug-level scale by a factor of three.[21]

Urban and Craig nomogram



Some have questioned the validity of all ODA nomograms because they are based on one-compartment parameters derived from traditional dosing methods. Some pk studies have shown that the pharmacokinetics of aminoglycosides at high doses differ significantly from those at traditional doses. Therefore, it is argued that nomograms based on an assumption of similar kinetics are invalid. [22]

VII. Bibliography

1. Devine B. Gentamicin therapy. Drug Intell Clin Pharm. 1974;8:650-655.
2. Sarubbi FA, Hull JW. Gentamicin serum concentrations: pharmacokinetic predicitions. Ann Intern Med 1976;85:183-189. [PubMed]
3. Sawchuk RJ, Zaske DE, Cipolle RJ, Wargin WA, Strate RG. Kinetic model for gentamicin dosing with the use of individual patient parameters. Clin Pharmacol Ther 1977;21;3:362-369. [PubMed]
4. Sarubbi FA, Hull JW. Amikacin serum concentrations: prediction of levels and dosage guidelines. Ann Intern Med 1978;89:612-618. [PubMed]
5. 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 Chemo 1995;29;3:650-655. [PubMed]
6. Blouin RA, et al. Tobramycin pharmacokinetics in morbidly obese patients. Clin Pharmacol Ther 1979;26:508-513. [PubMed]
7. Bauer LA, et al. Amikacin pharmacokinetics in morbidly obese patients. Am J Hosp Pharmacy 1980;37:519-522.
8. Korsager S. Administration of gentamicin to obese patients. Int J Clin Pharmacol Ther Tox 1980;18,12:549-553. [PubMed]
9. Lesar TS, Rotschafer JC, Strand LM, Solem LD, Zaske DE. Gentamicin dosing errors with four commonly used nomograms. JAMA 1982;248(10);1190-1193. [PubMed]
10. Sheiner LB, Beal S. Bayesian individualization of pharmacokinetics: simple implementation and comparison with non-Bayesian methods. J Pharm Sci 1982 71:1344-1348. [PubMed]
11. Matzke GR, Burkle WS, Lucarotti RL. Gentamicin and tobramycin dosing guidelines: an evaluation. Drug Intell Clin Pharm. 1983;17:425-432.
12. Burton ME, Brater DC, Chen PS, Day RB, Huber PJ, Vasko MR. A Bayesian feedback method of aminoglycoside dosing. Clin Pharmacol Ther 37:349-357, 1985. [PubMed]
13. Burton ME, Chow MS, Platt DR, Day RB, Brater DC, Vasko MR. Accuracy of Bayesian and Sawchuk-Zaske dosing methods for gentamicin. Clin Pharm 1986;5:143-149. [PubMed]
14. Fant WK. Controversies in antimicrobial therapy: Pitfalls in monitoring aminoglycoside therapy. AJHP 1986:43:641-645.
15. Chrystyn H. Validation of the use of Bayesian analysis in the optimization of gentamicin therapy. Drug Intell Clin Pharm. 1988 22:49-53. [PubMed]
16. Donahue T, Yates DJ. Predictability of aminoglycoside serum levels dosed by a pharmacy protocol. Hospital Pharmacy 1988:23;11-25
17. Rodvelt KA, Zokufa H, Rotschafer JC. Aminoglycoside pharmacokinetic monitoring: An integral part of patient care? Clin Pharm 1988:7:608-613. [PubMed]
18. Okamoto MP, Chi A, et al. Comparison of two microcoputer Bayesian pharmacokinetic programs for predicting serum gentamicin concentrations. Clin Pharm 1990 9:708-11. [PubMed]
19. Tsubaki T, Chandler MHH. Evaluating new and traditional methods for aminoglycoside dosing with various degrees of renal function. Pharmacotherapy 1994; 14:330-336. [PubMed]
20. Anaizi N. Once-daily dosing of aminoglycosides. A consensus document. Int J Clin Pharmacol Ther. 1997 Jun;35(6):223-6.
21. Urban AW, Craig WA. Daily dosage of Aminoglycosides. Current Clinical Topics in Infectious Diseases Vol 17, JS Remington & MN Swartz, Eds. Blackwell Science, Malden, MA, 1997. Full text from ClinRx.Com
22. Demczar DJ, Nafziger AN, Bertino JS. Pharmacokinetics of Gentamicin at Traditional versus High Doses: Implications for Once-Daily Aminoglycoside Dosing. Antimicrob Agents Chemother. 1997 41:1115-1119. [PubMed]
23. Casano RA, Johnson DF, Bykhovskaya Y, Torricelli F, Bigozzi M, Fischel-Ghodsian N. Inherited susceptibility to aminoglycoside ototoxicity: genetic heterogeneity and clinical

implications. Am J Otolaryngol. 1999 May-Jun;20(3):151-6. [PubMed]
24. Hutchin T, Cortopassi G. Proposed molecular and cellular mechanism for aminoglycoside ototoxicity. Antimicrob Agents Chemother. 1994 Nov;38(11):2517-20 Full text from aac.asm.org
25. Hain, TC. Bilateral vestibulopathy. July 2007.

VIII. Recommended Reading

1. Ambrose PJ, Winter ME. Vancomycin. In: Winter ME. Basic clinical pharmacokinetics, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
2. Bauer, Larry A. Applied Clinical Pharmacokinetics. McGraw-Hill. 2001.
3. Evans W, Schentag J, Jusko J (eds): Applied Pharmacokinetics 3rd edition. San Francisco, CA. Applied Therapeutics, 1992.

IX. Additional WWW Resouces

- A First Course in Pharmacokinetics and Biopharmaceutics
- RxKinetics Pharmacokinetics tutorial
- A PK/PD Approach to Antibiotic Therapy

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www.rxkinetics.com

RxKinetics, Plattsburg, MO 64477

This is a Norton safe site