The Pharmacodynamics of Aminoglycosides

Melinda K. Lacy, David P. Nicolau, Charles H. Nightingale, and Richard Quintiliani

From the Department of Pharmacy Practice, The University of Kansas Medical Center, Kansas City, Kansas; and the Division of Infectious Diseases and Office for Research Administration, Hartford Hospital, Hartford, Connecticut

Recently, a more complete understanding of the pharmacodynamics of aminoglycosides has been recognized, indicating that this class of antibiotics exhibits both concentration-dependent bactericidal activity and a postantibiotic effect. This pharmacodynamic information, along with better knowledge of the mechanisms responsible for aminoglycoside toxicity, established the foundation for once-daily aminoglycoside dosing regimens. This new approach to aminoglycoside dosing appears to be safe, efficacious, and cost-effective, resulting in its increasing popularity in clinical practice.

Although aminoglycoside antibiotics have been used successfully for >50 years [1], recent data suggest that the conventional dosing approach has not optimized bacterial killing. These recent observations, together with a more complete understanding of pharmacodynamics, have led to the application of new aminoglycoside dosing regimens [2, 3]. In this report we discuss the pharmacodynamics of aminoglycosides and the new dosing strategies for this class of antibiotics.

The in vitro antimicrobial spectrum of activity of the aminoglycosides includes a broad range of aerobic gram-negative bacilli, many staphylococci, and certain mycobacteria [4]. Aminoglycosides exert their bactericidal effects by irreversibly binding to the 30S ribosomal subunit of susceptible bacteria, which results in the inhibition of protein synthesis [4]. An energy- and oxygen-dependent transport mechanism is required for aminoglycosides to penetrate the outer bacterial membrane of susceptible bacteria [4]. It is for this reason that this class of antibiotics demonstrates poor activity against anaerobes and has decreased ability to penetrate the bacteria within abscesses that may have limited oxygen.

In general, the aminoglycosides are clinically used in the treatment of documented or suspected gram-negative infections and are often combined with β-lactams for extrarenal infections. In addition, aminoglycosides are used in combination with other antibiotics for synergy in the treatment of difficult infections, such as enterococcal endocarditis.

Bactericidal Activity

For antibiotics to kill bacteria, they must interact with a binding site, occupy a critical number of these sites, and remain at the binding site for a finite period of time [5]. The presence of the antibiotic prohibits normal biochemical reactions and, therefore, the organism dies. The concentration needed to occupy the critical number of sites necessary for this to occur is not known. However, an easily measured and probably proportional concentration, such as the MIC or the MBC, is used in its place.

It is also important to realize that the concentration of drug in the area of binding sites is controlled by drug concentration in the media in which bacteria reside, usually interstitial-like fluid. Antibiotics in such fluids have generally been found to rapidly become in equilibrium with the blood; therefore, antibiotic blood (serum, plasma) concentrations are an important parameter in bactericidal activity. Bactericidal activity is therefore a function of antibiotic concentration in the serum and the duration of time that antibiotic exists in the body.

In pharmacodynamic terms, one can say that bactericidal activity is a function of the time that serum concentrations remain above some critical value, i.e., the MIC. Pharmacokinetically, the product of concentration and time is termed the area under the serum-time curve (AUC), and therefore it is also true that bactericidal activity is a function of the AUC. Fortunately, this relationship can be simplified.

For concentration-independent-killing drugs such as β-lactams, the rate of bacterial killing is constant once a value of $\sim$2–4 times the MIC is reached. Under these conditions, the contribution made by the concentration component of the AUC ($Cp \times t$) is negligible and the pharmacokinetic relationship to bacterial killing is just a function of the time that concentrations remain above the MIC. As a result, the goal of therapy with these agents should be to maintain their concentration above the MIC against the infecting pathogen for as long as possible during any dosing interval [2].

Unlike the β-lactams, aminoglycosides have concentration-dependent antibacterial activity. This means that as drug concentrations rise, the rate of bacterial killing increases. It is possible that the concentration can be so high that all the organisms die within a short period of time. Under these circumstances the contribution of the time of exposure of bacteria to

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Reprints or correspondence: Dr. Charles H. Nightingale, Office for Research Administration, Hartford Hospital, 80 Seymour Street, P.O. Box 5037, Hartford, Connecticut 06102-5037.

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drug is no longer important to the killing process, and the eradication of bacteria is only a function of drug concentration.

Concentration-dependent activity of aminoglycosides has been demonstrated in several in vitro and in vivo animal studies [6–13]. While the exact concentration necessary for this simplification to occur is not known, a value of 10 times the MIC seems to be a generally accepted ratio of peak serum concentration to MIC; this will be discussed in more detail below. When the ratio is less than ~10, then the time of exposure of bacteria to drug cannot be ignored, and the entire AUC must be considered in pharmacodynamic evaluation. Therefore, the goal of therapy with aminoglycosides is to optimize peak concentrations by employing the highest possible dose consistent with toxicological considerations.

In accordance with these data, clinical studies have shown that higher aminoglycoside peak concentrations have been associated with increased survival and enhanced therapeutic response in the treatment of gram-negative bacteremia and pneumonia [14–17]. One clinical study demonstrated a relationship between serum aminoglycoside concentrations and the MIC of the organism [6]. These investigators found a graded dose-response effect between an increasing maximal peak concentration/MIC ratio and clinical response [6].

Other studies have shown that the peak aminoglycoside concentration/MIC ratio needs to be at least between 8:1 and 10:1 in order to maximize the bactericidal effects of these drugs [9–11, 18]. In addition to optimizing bactericidal activity, the peak/MIC ratio of 10:1 was associated with a decrease in the selection and regrowth of resistant subpopulations present in the initial inoculum [9].

Postantibiotic Effect

The postantibiotic effect (PAE) is defined as the persistent suppression of bacterial growth after limited exposure of organisms to an antibiotic [19–21]. Several factors are known to influence the presence and duration of the PAE. They include type of organism, class and concentration of antibiotic, duration of antimicrobial exposure, and antimicrobial combinations [21–23]. Drug-induced nonlethal damage is the probable mechanism of the PAE of aminoglycosides and β-lactams. Therefore, nonlethal damage by aminoglycosides would be caused by the irreversible binding to bacterial ribosomes [22, 23].

Generally, β-lactam antibiotics have PAEs against only gram-positive organisms [19, 21], while aminoglycosides exhibit a PAE on both gram-positive and gram-negative organisms [7, 11, 19–26]. A definite correlation between increased concentration of aminoglycoside and longer duration of the PAE has been reported [24, 26]. It has been shown in in vitro and animal studies that the duration of the PAE can vary with subsequent doses [27, 28]. Furthermore, the PAE duration is variable for different types of bacteria. A range of 0.5–7.5 hours has been reported in the literature for aminoglycosides [7, 24].

Adaptive and Selective Resistance

Adaptive resistance is the decreased drug uptake that occurs in bacteria that survive an initial, suboptimal aminoglycoside dose [29]. This process has been shown to occur in several in vitro and animal studies reported in the literature [11, 30, 31]. One study showed that once-daily dosing of amikacin, in comparison with q12h dosing, helped maintain its bactericidal activity against isolates of *Pseudomonas aeruginosa* [32]. Thus, drug regimens that allow for longer drug-free intervals should help protect the bactericidal activity of aminoglycosides by decreasing adaptive resistance. High-dose aminoglycoside therapy, if properly designed (i.e., with peak-to-MIC ratios of ~10), helps suppress the survival of high-MIC mutants within a population of generally susceptible organisms. The lack of emergence of resistant organisms during therapy is a major advantage to high-dose aminoglycoside regimens.

Aminoglycoside Therapy with Extended Dosing Intervals

With regard to the pharmacodynamic profile of aminoglycosides, several advantages of using extended dosing intervals are readily apparent. As stated previously, giving aminoglycosides as a single daily dose, as opposed to using conventional dosing strategies, provides the opportunity to maximize the peak concentration/MIC ratio and the resultant bactericidal activity. In addition, the PAE may also allow for longer periods of bacterial suppression during the dosing interval. Lastly, this aminoglycoside dosing approach may prevent the development of bacterial resistance and reduce the potential for toxicity [33].

Once-daily aminoglycoside (ODA) therapy has been evaluated in several large clinical studies, some with a total study population of $\geqslant$100 patients [34–43]. Of those that compared ODA with multidose aminoglycoside regimens by study design, ODA was shown to be as efficacious or superior to traditional dosing for the treatment of a wide variety of infections [34–41]. Toxicity evaluations showed that there were no differences between the two dosing methods with regard to nephrotoxicity [34–41] or ototoxicity [34, 36–41].

Seven of the large trials included doses of 5.5 mg/kg or higher of netilmicin [34, 39, 43] or 15 mg/kg or higher of amikacin [36, 37, 41, 42]. In addition, two of the studies were of neutropenic patients and showed that ODA therapy maintained its efficacy [39, 40]. Furthermore, a recent report from one hospital using an ODA protocol (7 mg/kg dosing for gentamicin or tobramycin) indicates that no adverse outcomes have been noted in 496 patients that have undergone ODA regimens [44].

Several recently published meta-analyses of clinical trials evaluating ODA dosing with standard dosing regimens also demonstrate that increased bacterial killing and trends for decreased toxicity are actually borne out in clinical practice when extended-interval dosing is used [45–54].

At Hartford Hospital (Hartford, CT), ODA therapy has been used since October 1992 [3], for >3,500 patients. A fixed iv dose of 7 mg/kg is utilized, and either a special nomogram and a single serum level determination or a creatinine clearance calculation determines the dosing interval. This dose was selected on the basis of pharmacokinetic modeling designed to obtain a target peak concentration of 20 μg/mL. This concentration was selected since it is 10 times the average MIC (2 μg/mL) of *P. aeruginosa* at this institution and because aminoglycosides are commonly used to treat proven or suspected infections caused by this organism.

Another reason for using this dose, aside from optimizing bacterial eradication, is to decrease toxicity due to saturation of the capacity-limited tissue-uptake mechanism for aminoglycosides [33]. It is likely that a 5-mg/kg dose would also saturate the uptake mechanism; however, if that is true, no additional toxicity would result from the higher dose since tissue accumulation would be at a maximum. While the 5-mg/kg dose would likely result in the same degree of toxicity, it may not achieve optimum peak-to-MIC ratios.

It can be argued that aminoglycosides are usually used in combination with other antibiotics such as β-lactams and that it is not necessary to optimize the aminoglycoside dose. This may be true but is somewhat speculative. The approach with use of a 7-mg/kg dose is more conservative in that it considers the worst-case scenario and doses accordingly.

ODA therapy has been used for many types of infections, including intraabdominal, pulmonary, genitourinary, skin, and soft tissue, as well as staphylococcal and streptococcal endocarditis. According to program criteria at Hartford Hospital, ODA therapy is not administered to adult patients with ascites, patients with burns over >20% of their body surface area, pregnant patients, those on dialysis for end-stage renal disease, or patients with enterococcal endocarditis. Immunocompromised patients are not excluded from receiving ODA.

Actually, the term ODA is a misnomer, since it involves the use of high doses of aminoglycosides to maximize effectiveness and minimize therapy and dosing of the drug at infrequent intervals to maximize the washout period and further decrease the potential for toxicity. The goal in establishing an adequate dosing interval is based upon the assumption that the washout period should be between 4 and 10 hours. When the washout period is <4 hours, the dosing interval is extended. In such cases, a nomogram is used to determine the appropriate dosing interval on the basis of an aminoglycoside serum concentration. Individualized pharmacokinetic analysis is performed in situations where the nomogram indicates that dosing intervals of >48 hours are needed. Since the dosing interval varies with time, this program cannot technically be called an ODA program.

An ongoing audit of ODA therapy has shown that toxicity has remained at very low levels, despite the fact that 24% of treated patients were >70 years of age and 37% of all patients underwent therapy for ⩾6 days, among a population of 2,184 patients [3]. The incidence of nephrotoxicity was lower with ODA than it has been historically (1.2% vs. 3%–5%). Of the patients treated, two had clinical evidence of vestibular toxicity while hospitalized.

Of the 59 patients who were prospectively followed, all receiving ODA therapy for extrapulmonary infections were clinically and microbiologically cured [3]. Clinical cure was noted in 86% (25) of 29 patients with pulmonary infections, while the microbiologic cure rate in this population was 40% (5 of 13), reflecting a low rate of definitive bacteriologic diagnosis. Length of therapy was similar between ODA and traditional dosing regimens.

As a result of the ODA program implementation, annual hospital savings in excess of $100,000 (U.S.) are being realized because of decreased supply and labor costs, less frequent determinations of serum drug concentrations, and decreased nephrotoxicity [55, 56].

Summary

The pharmacodynamics of aminoglycosides have been shown to be maximized when high-dose, extended-interval aminoglycoside therapy is employed. As a result, the implementation of such a program should optimize potential for clinical cure and minimize toxicity, and it may help to prevent the development of resistance. Although such dosing is not appropriate for all patients, this strategy appears to be useful in the majority of patients requiring aminoglycoside therapy and can be successfully employed as a hospital-wide program. With most programs, provisions must be made for physicians to deviate from the general program when the needs of the patient so dictate.

References

1. Gilbert DN. Aminoglycosides. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's principles and practice of infectious diseases. 4th ed. New York, NY: Churchill Livingstone, **1995**:279.
2. Ebert SC, Craig WA. Pharmacodynamic properties of antibiotics: application to drug monitoring and dosage regimen design. Infect Control Hosp Epidemiol **1990**;11:319–26.
3. 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**;39:650–5.
4. Edson RS, Terrell CL. The aminoglycosides. Mayo Clin Proc **1991**;66:1158–64.
5. Nightingale CH, Quintiliani R, Nicolau DP. Intelligent dosing of antimicrobials. Curr Clin Top Infect Dis **1994**;14:252–65.

6. 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**;155:93–9.
7. Begg EJ, Peddie BA, Chambers ST, Boswell DR. Comparison of gentamicin dosing regimens using an in-vitro model. J Antimicrob Chemother **1992**;29:427–33.
8. MacArthur RD, Lolans V, Zar FA, Jackson GG. Biphasic, concentration-dependent and rate-limited, concentration-independent bacterial killing by an aminoglycoside antibiotic. J Infect Dis **1984**;150:778–9.
9. Blaser J, Stone BB, Groner MC, Zinner SH. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. Antimicrob Agents Chemother **1987**;31:1054–60.
10. Jackson GG, Lolans VT, Daikos GL. The inductive role of ionic binding in the bactericidal and postexposure effects of aminoglycoside antibiotics with implications for dosing. J Infect Dis **1990**;162:408–13.
11. Daikos GL, Jackson GG, Lolans VT, Livermore DM. Adaptive resistance to aminoglycoside antibiotics from first-exposure down-regulation. J Infect Dis **1990**;162:414–20.
12. Staneva M, Markova B, Atanasova I, Terziivanov D. Pharmacokinetic and pharmacodynamic approach for comparing two therapeutic regimens using amikacin. Antimicrob Agents Chemother **1994**;38:981–5.
13. Kapusnik JE, Hackbarth CJ, Chambers HF, Carpenter T, Sande MA. Single, large, daily dosing versus intermittent dosing of tobramycin for treating experimental pseudomonas pneumonia. J Infect Dis **1988**;158:7–12.
14. Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. J Infect Dis **1984**;149:443–8.
15. Noone P, Parsons TMC, Pattison JR, Slack RCB, Garfield-Davies D, Hughes K. Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. BMJ **1974**;1:477–81.
16. Anderson ET, Young LS, Hewitt WL. Simultaneous antibiotic levels in ''breakthrough'' gram-negative rod bacteremia. Am J Med **1976**;61:493–7.
17. Moore RD, Smith CR, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. Am J Med **1984**;77:657–62.
18. Deziel-Evans LM, Murphy JE, Job ML. Correlation of pharmacokinetic indices with therapeutic outcome in patients receiving aminoglycosides. Clin Pharm **1986**;5:319–24.
19. Bundtzen RW, Gerber AU, Cohn DL, Craig WA. Postantibiotic suppression of bacterial growth. Rev Infect Dis **1981**;3:28–37.
20. Vogelman B, Craig WA. Kinetics of antimicrobial activity. J Pediatr **1986**;108:835–40.
21. Zhanel GG, Hoban DJ, Harding GKM. The postantibiotic effect: a review of in vitro and in vivo data. Ann Pharmacother **1991**;25:153–63.
22. Craig WA, Vogelman B. The postantibiotic effect. Ann Intern Med **1987**;106:900–2.
23. Vogelman BS, Craig WA. Postantibiotic effects. J Antimicrob Chemother **1985**;15(suppl A):37–46.
24. 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**;157:287–98.
25. Gerber AU, Wiprachtiger P, Stettler-Spichiger U, Lebek G. Constant infusions vs. intermittent doses of gentamicin against *Pseudomonas aeruginosa* in vitro. J Infect Dis **1982**;145:554–60.
26. Hessen MT, Pitsakis PG, Levison ME. Postantibiotic effect of penicillin plus gentamicin versus *Enterococcus faecalis* in vitro and in vivo. Antimicrob Agents Chemother **1989**;33:608–11.
27. McGrath BJ, Marchbanks CR, Gilbert D, Dudley MN. In vitro postantibiotic effect following exposure to imipenem, temafloxacin, and tobramycin. Antimicrob Agents Chemother **1993**;37:1723–5.
28. Odenholt-Tornqvist I. Pharmacodynamics of beta-lactam antibiotics: studies on the paradoxical effect and postantibiotic effects in vitro and in an animal model. Scand J Infect Dis Suppl **1989**;58:1–55.
29. Preston SL, Briceland LL. Single daily dosing of aminoglycosides. Pharmacother **1995**;15:297–316.
30. Daikos GL, Lolans VT, Jackson GG. First-exposure adaptive resistance to aminoglycoside antibiotics in vivo with meaning for optimal clinical use. Antimicrob Agents Chemother **1991**;35:117–23.
31. Gerber AU, Vastola AP, Brandel J, Craig WA. Selection of aminoglycoside-resistant variants of *Pseudomonas aeruginosa* in an in vivo model. J Infect Dis **1982**;146:691–7.
32. McGrath BJ, Lamp KC, Rybak MJ. Pharmacodynamic effects of extended dosing intervals of imipenem alone and in combination with amikacin against *Pseudomonas aeruginosa* in an in vitro model. Antimicrob Agents Chemother **1993**;37:1931–7.
33. Verpooten GA, Giuliano RA, Verbist L, Eestermans G, DeBroe ME. Once-daily dosing decreases renal accumulation of gentamicin and netilmicin. Clin Pharmacol Ther **1989**;45:22–7.
34. DeVries PJ, Verkooyen RP, Leguit P, Verbrugh HA. Prospective randomized study of once-daily versus thrice-daily netilmicin regimens in patients with intraabdominal infections. Eur J Clin Microbiol Infect Dis **1990**;9:161–8.
35. Mauracher EH, Lau WY, Kartowisastro H, et al. Comparison of once-daily and thrice-daily netilmicin regimens in serious systemic infections: a multicenter study in six Asian countries. Clin Ther **1989**;11:604–13.
36. Maller R, Ahrne H, Eilard T, et al. Efficacy and safety of amikacin in systemic infections when given as a single daily dose or in two divided doses. J Antimicrob Chemother **1991**;27(suppl C):121–8.
37. Maller R, Ahrne H, Holmen C, et al. Once- versus twice-daily amikacin regimen: efficacy and safety in systemic gram-negative infections. J Antimicrob Chemother **1993**;31:939–48.
38. Prins JM, Buller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. Lancet **1993**;341:335–9.
39. Rozdzinski E, Kern WV, Reichle A, et al. Once-daily versus thrice-daily dosing of netilmicin in combination with β-lactam antibiotics as empirical therapy for febrile neutropenic patients. J Antimicrob Chemother **1993**;31:585–98.
40. TerBraak EW, DeVries PJ, Bouter KP, et al. Once-daily dosing regimen for aminoglycoside plus β-lactam combination therapy of serious bacterial infections: comparative trial with netilmicin plus ceftriaxone. Am J Med **1990**;89:58–66.
41. International Antimicrobial Therapy Cooperative Group of the EORTC. Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. Ann Intern Med **1993**;119:584–93.
42. Beaucaire G, Leroy O, Beuscart C, et al. Clinical and bacteriological efficacy, and practical aspects of amikacin given once daily for severe infections. J Antimicrob Chemother **1991**;27(suppl C):91–103.
43. Prins JM, Buller HR, Kuijper EJ, Tange RA, Speelman P. Once-daily gentamicin versus once-daily netilmicin in patients with serious infections—a randomized clinical trial. J Antimicrob Chemother **1994**;33:823–35.
44. Self RM. Daily aminoglycoside update. P & T **1995**;20:495–6.
45. Galløe AM, Graudal N, Christensen HR, Kampmann JP. Aminoglycosides: single or multiple daily dosing? A meta-analysis on efficacy and safety. Eur J Clin Pharmacol **1995**;48:39–43.
46. Freeman CD, Strayer A. Comparative incidence of nephrotoxicity with once-daily aminoglycosides (ODA) versus multiple daily dosing (MDA): a meta-analysis [abstract no 95]. In: Program and abstracts of the American College of Clinical Pharmacy 1995 Annual Meeting. Pharmacotherapy **1995**;15:376.

47. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. Ann Intern Med **1996**;124: 717–25.
48. Barza M, Ioannidis JPA, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. BMJ **1996**;312: 338–45.
49. Freeman CD, Strayer AH. Mega-analysis of meta-analysis: an examination of meta-analysis with an emphasis on once-daily aminoglycoside comparative trials. Pharmacotherapy **1996**;16:1093–102.
50. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. J Antimicrob Chemother **1996**;37:645–63.
51. Ferriols-Lisart R, Alos-Alminana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. Am J Health Syst Pharm **1996**; 53:1141–50.
52. Bailey TC, Little JR, Littenberg B, Reichley RM, Dunagan WC. A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis **1997**;24:786–95.
53. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis **1997**;24:796–809.
54. Hatala R, Dinh TT, Cook DJ. Single daily dosing of aminoglycosides in immunocompromised adults: a systematic review. Clin Infect Dis **1997**; 24:810–5.
55. Nicolau DP, Wu AHB, Finocchiaro S, et al. Once-daily aminoglycoside dosing: impact on requests and costs for therapeutic drug monitoring. Ther Drug Monit **1996**;18:263–6.
56. Hitt CM, Klepser ME, Nightingale CH, Quintiliani R, Nicolau DP. Pharmacoeconomic impact of a once-daily aminoglycoside program. Pharmacotherapy **1997**;17:810–14.