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Aminoglycoside antibiotics are first-line treatment for many infectious diseases in the pediatric population and are effective in adults. The traditional dosing interval in children is every 8–12 hours. Studies in adults reported equivalent efficacy and equal or less toxicity with once-daily regimens. Despite many studies in the adult population, this approach has yet to become standard practice in most pediatric hospitals. Reasons for lack of acceptance of this strategy in children include rapid aminoglycoside clearance, unknown duration of postantibiotic effect, safety concerns, and limited clinical and efficacy data.

Aminoglycoside antibiotics are first-line treatment for many gram-negative infections in children. Over the past several years, studies performed in adults changed the manner in which these drugs are dosed. Traditionally, aminoglycosides were administered several times/day to both adults and children. Data from adult studies indicate the safety and efficacy of once-daily dosing (ODD) and prompted some clinicians to change to that practice. Results of randomized trials and meta-analyses in adults indicate that ODD is no less effective than traditional dosing and may be associated with an equal or lower frequency of nephrotoxicity.[1-13]

According to one study, extended-interval aminoglycoside dosing was used in 75% of all acute care hospitals responding to a mailed questionnaire.[14] Although ODD has become prevalent in many adult settings, it is not widely used in the pediatric setting. Of hospitals responding to the questionnaire, only 23% used extended-interval dosing for patients aged 1- 18 years.[14] Several questions arise when contemplating ODD in children; namely, optimum dosage, interval, and monitoring. Other important considerations are efficacy, safety, and length of time that serum concentrations are below the minimum inhibitory concentration (MIC) for the microorganism.

Pharmacology

Mechanism of Action

Aminoglycosides as a class have bactericidal activity against a broad spectrum of gram negative organisms, including Pseudomonas aeruginosa. By irreversibly binding to the 30S bacterial ribosome, the agents inhibit bacterial protein synthesis. This action requires an energy- and oxygen-dependent transport mechanism into the bacterial cell.[15]

Pharmacodynamics

Unlike β-lactam antibiotics, which require a continuous time above MIC for maximum bacterial killing, bactericidal activity of aminoglycosides is concentration dependent. [15–17] As the peak serum concentration of the drug increases, bacterial killing is increased. It is not known at what peak serum concentration bacterial killing is maximized. In early studies, peak concentrations greater than 5 μg/ml for gentamicin and tobramycin, and greater than 20 μg/ml for amikacin were associated with decreased mortality from gram-negative bacteremia.[18] In addition,

successful outcome from gram-negative pneumonia was significantly increased in patients with peak serum concentrations of 7 μg/ml or more for gentamicin and tobramycin and 28 μg/ml for amikacin. 19 In one study clinical cure of gram-negative pneumonia was greatest when gentamicin peak concentrations were 8 μg/ml or more. 20 Clinical cure was 89% compared with 43% in patients with a peak concentration of 8 μg/ml or more, and less than 8 μg/ml, respectively. 20 Subsequent studies reported that the serum peak concentration:MIC ratio (peak:MIC) rather than peak concentration alone was more strongly associated with a positive clinical response in patients infected with gram- negative organisms.21 Clinical response rates of approximately 90% could be achieved with a peak:MIC ratio between 8 and 10:1. 21 The theory is that bactericidal effects of aminoglycosides with traditional dosing can be maximized when the ratio is between 8 and 10:1. 16, 22This ratio may not be achieved consistently when traditional dosing is used for organisms that are intermediately susceptible or resistant to the drugs; however, it should be achieved more reliably with ODD.

Adaptive Resistance

Adaptive resistance is a reversible diminished bacterial response to aminoglycosides appearing after first exposure of bacteria to the drug. Aminoglycosides have biphasic bactericidal kinetics. The initial phase invokes rapid concentration-dependent bacterial killing, and the second phase is characterized by slow concentration-independent bacterial killing. [23–26] Adaptive resistance develops during the second phase due to downregulation of drug uptake into the bacterial cell and causes impermeability to all aminoglycosides. 23, 24 It was first shown by in vitro studies with *P. aeruginosa* strains. [23] It also developed in vivo in neutropenic mice exposed to netilmicin 30 mg/kg after start of infection. [24] The three study groups were not redosed, given one additional 20-mg/kg dose, or given a 20-mg/kg dose every 2 hours for five doses. The first and second (of five) doses of netilmicin reduced the number of colony-forming units (cfu), but the three additional doses given 4, 6, and 8 hours after the first dose produced no detectable bacterial killing. [24] The cfu/mouse thigh began to increase 6 hours after the first drug exposure despite a plasma concentration above MIC. [24] The unresponsiveness to additional netilmicin doses was reversed within 8 hours of the final dose.

The mouse half-life of netilmicin in that study was 25 minutes or less. 24 Dosing aminoglycosides once every 4–5 half-lives in mice simulates comparable dosing of every 8 hours in children and adolescents. This is based on knowledge that the agents' half-lives in children and adolescents with normal renal function are approximately 1.5–2.5 hours. [27] Therefore, the theoretical clinical implication of adaptive resistance studies is that maintaining the aminoglycoside concentration persistently above MIC may provide no additional benefit.

A relatively drug-free interval may reduce or reverse adaptive resistance and may improve bacterial killing. In our experience, trough concentrations with traditional dosing in children sometimes may fall below MIC, but concentrations that are equal to or above MIC also have been observed. Comparatively, ODD can more reliably achieve a relatively drug-free interval due to extended dosing intervals. In this setting, traditional dosing theoretically would not have additional bactericidal benefit. In addition, it would have less potential to reduce or reverse the development of adaptive resistance.

As adaptive resistance has been studied only in vitro and in animal models, it is unclear whether this relatively drug-free interval with ODD will offer a therapeutic advantage. The optimal length of this drug-free interval has not been identified. If it is excessive, it actually may result in clinically significant bacterial regrowth even to the level of the first bacterial inoculum. 24 It is possible that ODD could prolong the drug-free interval given the short half- lives of aminoglycosides in children.

Postantibiotic Effect

The postantibiotic effect (PAE) is persistence of antimicrobial action with minimal concentration of drug. [28, 29] It originally was observed in vitro but also was seen in in vivo animal studies. Although it is thought to occur in humans, a significant in vivo PAE in humans has not been demonstrated. A number of factors such as type of organism, drug concentration, and class of antimicrobial can effect the duration of the PAE.[29] Aminoglycosides have a significant PAE with gram-negative organisms. In neutropenic mice, the PAE duration for various gram-negative organisms was 1.4–7.3 hours after gentamicin 8 mg/kg. 3 Strains of *Klebsiella pneumonia* have consistently longer PAEs than strains of *Escherichia coli*.[30, 31] In addition, increased doses of tobramycin led to longer PAEs for *P. aeruginosa* and K. pneumonia in mice. 31 Data in humans are limited. After doses of amikacin 15 and 30 mg/kg, the in vitro PAE duration for gram-negative organisms ranged from 1 to more than 2 hours in humans. [32] This study also showed a direct relationship between drug concentration and PAE.

Toxicity

Nephrotoxicity

A significant concern with aminoglycosides in adults as well as children is nephrotoxicity. Few data are available on the frequency or clinical impact of nephrotoxicity in children receiving traditionally dosed aminoglycosides. The disorder occurs as a result of an interaction of the drug in the renal tubule, causing reversible tubular necrosis and decreased glomerular filtration.[15, 33] One hypothesis regarding the mechanism is that a small portion of the aminoglycoside is stored in the tubular cell lysosome after reabsorption from the proximal tubule. Toxicity is then dependent on the local concentration within the lysosome. Another hypothesis is that once the drug concentration in the lysosome reaches a threshold level, the drug is released and directly causes cellular toxicity. [33, 34]

Uptake of certain aminoglycosides is a saturable process. [34–36] Cortical uptake of netilmicin and gentamicin was saturable in rats, and compared with single injections, continuous infusions led to 30% and 50% higher cortical concentrations, respectively. [34] In contrast, renal cortex accumulation of tobramycin did not have saturable kinetics in rats but was linearly related to serum concentrations. [35] In humans, however, cortical concentrations of tobramycin were lower after single injections than multiple injections or continuous infusions. [36] Renal cortex concentrations of gentamicin, amikacin, and netilmicin were lower in humans after administration of identical daily doses as single injections versus multiple injections or continuous infusions. [35, 36] Area under the curve (AUC) was not significantly different among

dosing methods. [34, 36] Renal accumulation and toxicity of aminoglycosides in humans may be decreased with one daily dose based on evidence of saturable cortical uptake. Increased trough serum concentrations of aminoglycosides are directly related to nephrotoxicity, but high peak serum concentrations are not.[37] Other risk factors are duration of therapy, daily drug AUC, and concurrent nephrotoxic drugs. [37–39] Studies that compared ODD with traditional dosing in adults reported either a decreased frequency or no difference in nephrotoxicity.[1–13, 38, 39]

Ototoxicity

Another significant adverse effect of aminoglycosides is ototoxicity. As with nephrotoxicity, data are lacking regarding this adverse effect and its frequency in children. All drugs in this class may induce ototoxicity that can manifest as cochlear or vestibular symptoms. [15] The exact mechanism is not known but is thought to be an interaction between the agents and hair cell membranes in cochlear and vestibular receptors.[40,41] The interaction causes degenerative changes in the hair cell, possibly altering its structure and permeability. Many risk factors for ototoxicity have been proposed and/or identified, including aminoglycoside accumulation, renal impairment, length of therapy, age, dosage, and concurrent administration of ototoxic agents. [42] The literature has not clearly established the relationship, if any, between peak and trough concentrations and auditory or vestibular toxicity.

One study examined the relationship of a number of factors with aminoglycoside associated ototoxicity. [43] Data were collected on peak and trough serum drug concentrations, total dose, duration of therapy, age, and other factors. After logistic regression, only older age was a significant risk factor for this side effect. [43]

Rationale for Once-Daily Dosing

Traditionally, aminoglycoside antibiotics were dosed several times/day. Dosing in children with normal renal function is usually every 8 hours but is occasionally every 6 hours. The agents generally are given less frequently in term and preterm neonates due to decreased and possibly underdeveloped renal function. [27] The rationale for ODD in patients with normal renal function is based on pharmacodynamic principles inherent to aminoglycosides, especially two key points.

First, higher peak serum concentrations will be achieved with administration of higher doses. Since the drugs' bactericidal effect is related to peak concentrations, higher doses will achieve a higher peak concentration and ensure efficacy of therapy. With this dosing, it is possible to achieve the desired peak:MIC ratio of 8–10:1 even for intermediately susceptible organisms with high MICs. This ratio may not always be achievable with traditional dosing, especially if treating intermediately susceptible organisms. Even though the exact duration of the PAE in humans is questionable, efficacy of ODD is comparable to traditional dosing. As mentioned, administration every 24 hours should, in theory, minimize development of adaptive resistance. [23, 24]

Second, it is thought that ODD may reduce the frequency of nephrotoxicity since low or undetectable trough concentrations will be attained. The rationale of ODD seems logical based on the key points presented. However, many questions remain regarding ODD in infants, children, and adolescents.

Efficacy in Children

Extended-interval aminoglycoside dosing was studied in approximately 700 infants and children over 1 month of age (Table 1). [6, 11, 44–56] This regimen also was investigated in neonates up to 1 month of age but is not discussed here due to the decreased renal function in that patient population. Infectious processes included neutropenic fever, suspected or confirmed gram-negative infections, cystic fibrosis, and suspected or confirmed surgical infections. Nine studies evaluated clinical and/or microbiologic efficacy of ODD in approximately 450 children (Table 2). [44–51] It is important to note that the studies were not adequately powered to show a true statistical difference due to a limited number of subjects.

Clinical Efficacy

Five studies compared the clinical efficacy of aminoglycosides administered as one or multiple daily doses. [44–48] Three of them examined gentamicin, and one each tobramycin and amikacin. Clinical cure rates ranged from 88–92% and 90–98% in patients receiving once- daily and multiple daily doses, respectively. Clinical cure was achieved in 141 (93%) of 151 and 145 (95%) of 153 patients, respectively. 44–47 Two trials [44, 45] considered clinical cure to be resolution of signs and symptoms of infection. One defined the need for alternative parenteral antibiotics as either clinical failure or complication of original therapy. [44] Other trials defined failure to respond as persistence of fever and continuing neutropenia after the fifth and fourth days of therapy. [46, 47] One group did not report clinical cure rates, only clinical improvement. [48]

Four additional studies evaluating clinical efficacy did not compare dosing regimens, but administered aminoglycosides only once/day. [49–52] In one trial, 76% of febrile episodes (86/113) responded to first-line treatment (gentamicin plus ceftriaxone) with resolution of fever after 48 hours. [49] The remaining 24% of patients required vancomycin and ceftazidime due to unresolved fever with or without the presence of organisms resistant to first-line agents. [49] Others demonstrated 92% of febrile episodes (272/303) resolving clinically without a change in empiric antibiotic treatment. [50] Similarly, a clinical cure rate of 100% (25/25) was achieved in patients treated with once-daily amikacin. [51] In the final trial, 98% of patients receiving once-daily amikacin had a satisfactory clinical response after the end of treatment; however, some patients required additional oral (27%) or parenteral (14%) antimicrobial therapy. [52]

Microbiologic Efficacy

Of studies comparing ODD with traditionally dosed aminoglycosides, only two evaluated microbiologic as well as clinical efficacy. [44, 45] In one investigation, bacteriologic eradication rates were 97% (58/60) and 98% (58/59), respectively, in patients treated with gentamicin once/day and 3 times/day. [44] *Escherichia coli* was the most common causative organism for both groups. Other organisms were gram-negative *bacilli*, *enterococci*, and *Staphylococcus* sp. *Staphylococcus epidermidis* was observed in two patients treated once/day and one treated 3 times/day. In all of these patients, the organism was isolated in the absence of pyuria. The investigators considered none of the reinfection cases to be clinically significant. Similarly,

microbiologic cure was achieved in 100% (10/10) and 92% (12/13) of patients treated with gentamicin once/day and 3 times/day; data regarding reinfection were not reported. [45]

Table 1. Once-Daily Aminoglycoside Studies in Children

Age (yrs), Mean ± SD or Range	Population (no. of patients)	Drug Regimen	Peak Concentration (μg/ml), Mean ± SD [range]	Trough Concentration, (μg/ml), Mean ± SD [range]
8.9 ± 5.2[54]	Suspected surgical infection (31)	Gentamicin 7.5 mg/kg q24h	20.4 ± 45.4	0.29 ± 0.02
5.7 ± 4.9[54]	Suspected surgical infection (17)	Gentamicin 2.5 mg/kg q8h	7.2 ± 8.2	0.69 ± 0.13
8.7 (3 mo–20 yrs)[50]	Neutropenic or nonneutropenic fever with cancer (303 episodes/155 pts)	Amikacin 15 mg/kg q24h	23.9 ± 10.1, 10% of peaks > 40, 55% of peaks < 25	0.6, 85% below measurable limits
10–14[55]	Cystic fibrosis (7)	Tobramycin 8 mg/kg once	21.9 [16.7–25.9]	12 hrs after dose: < 2
10–14[55]	Cystic fibrosis (7)	Tobramycin 15 mg/kg q24h	40.2 [32.3–56.6]	24 hrs after dose: < 1
1 mo–12[44]	Urinary tract infection (90, q24h; 89, q8h)	Gentamicin q24h[a] Gentamicin q8h[a]	17.3 ± 5 6.4 ± 1.7	0.35 ± 0.89 0.55 ± 0.69
6.6 ± 4.7[45]	Suspected gram-negative infection (32)	Gentamicin 4.5 mg/kg q24h	13.9 [9.9–18.2]	0.2 [0–0.5]
4.7 ± 4.2[45]	Suspected gram-negative infection (31)	Gentamicin 1.5 mg/kg q8h	5.7 [3.4–8.5]	0.9 [0.4–1.5]
6.8 (3 mo–14 yrs)[52]	Gram-negative infection (56)	Amikacin 20 mg/kg q24h	36.5 [20.8–52.7]	Mean concentration 12 hrs after dose: 1.0 [0.1–4.6]
9.2 ± 5.3[46]	Febrile neutropenia (10)	Amikacin 20 mg/kg q24h	42.6 ± 12.6	0.18 ± 0.24
5.1 ± 3.5[46]	Febrile neutropenia (13)	Amikacin 10 mg/kg q12h	19.1 ± 12.3	0.85 ± 0.74
7.7 ± 4.4[47]	Febrile neutropenia (22)	Gentamicin 5 mg/kg q24h	11.5 [3.3–22], 77% of peaks > 10	0.18 [0.1–0.6]
6.6 ± 4.1[47]	Febrile neutropenia (30)	Gentamicin 5 mg/kg/day, divided q8h	5.2 [1.2–10], 44% of peaks > 6	0.8 [0.2–3.3]
1.6–18[56]	Nonneutropenic fever with cancer (18)	Gentamicin 6 mg/kg once	13.3 [6.8–20]	Mean concentration 16 hrs after dose: 0.3 [0.1–0.8]
1.6–18[56]	Neutropenic fever with cancer (73 episodes/54 pts)	Gentamicin 7 mg/kg q24h	17.2 [9.5–27.7]	Mean concentration 12 hrs after dose: 0.9 [0.1–3.7]
6 mo–16 yrs[49]	Febrile neutropenia (113 episodes/59 pts)	Gentamicin 7 mg/kg q24h	No mean peak reported [5.2–37.2]	8 hrs after dose: (102/110 episodes [93%]) < 2
3 mo–14 yrs[51]	Gram-negative infection (25)	Amikacin 20 mg/kg q24h	Day 1: 52 ± 11.8 Day 4: 53.6 ± 11.9	Day 1: 6.8 ± 3.4 Day 4: 6 ± 1.4
11.4 ± 4.2[48]	Cystic fibrosis (12)	Tobramycin 15 mg/kg q24h	Day 1: 42.5 ± 11.2 Day 14: 39.4 ± 20	Day 1: 0.3 ± 0.2 Day 14: 0.4 ± 0.3
10.7 ± 2.9[48]	Cystic fibrosis (10)	Tobramycin 5 mg/kg q8h	Day 1: 13.2 ± 7.1 Day 14: 12.4 ± 3.9	Day 1: 0.3 ± 0.2 Day 14: 0.4 ± 0.3
2–13[53]	Febrile neutropenia (16 episodes/13 pts)	Amikacin 20 mg/kg q24h	36.9 ± 9.6	Median concentration 6, 12, and 24 hrs after dose: < 3

[a]Daily doses (mg/kg): 7.5 (< 5 yrs), 6.0 (5–10 yrs), 4.5 (> 10 yrs).

In the most detailed data regarding microbiologic efficacy, 56 patients with documented bacterial infection received amikacin once/day either alone or in combination with another antibiotic.[52] Six classifications of infections were pneumonia (16 patients); chronic otitis (7); meningitis, bacteremia, septicemia (9); osteomyelitis (12); pyelonephritis (7); and peritonitis (5). Infecting

organisms were *Pseudomonas* sp (27), *Enterobacter* sp (4), *E. coli* (12), *Klebsiella* sp (2), *Acinetobacter* sp (8), and *Haemophilus influenzae* (5). Some patients had multiorganism infections. Concomitant antimicrobials with expanded gram-negative or gram-positive spectra of activity were administered to 71% and 21% of patients, respectively. Bacterial eradication occurred in 49 (89%) of 55 patients. Six patients had persistently positive cultures after treatment and one was unevaluable.

Microbiologic cure in patients with a variety of gram-negative infections was 100% (25/25) in one study.51 Cultures grew *E. coli* (18), *K. pneumoniae* (4), *Enterobacter* sp (1), *Providencia* sp (1), and *P. aeruginosa* (1). Another group reported 99 positive cultures in 96 (32%) of 303 febrile episodes.50 Of note, 85 of those 99 cultures were documented bacteremia. *Staphylococcus epidermidis* accounted for 47% (40/85) and gram-negative organisms for only 22% (19/85) of positive blood cultures. Treatment failed in 14% (13/96) of culturepositive episodes, and in 36% and 8% ($p<0.001$) of gram-negative and gram-positive infections, respectively.50 Positive blood cultures isolated one or more organisms in 29 (25%) of 113 febrile neutropenic episodes, but microbiologic efficacy was not evaluated.[49]

Table 2. Clinical and Microbiologic Efficacy with Once-Daily Aminoglycoside Dosing in Children

	No. (%) of Patients		
Drug	Clinical Efficacy	Microbiologic Efficacy	Concomitant Antibiotics
Amikacin[50]	Cure 169/174 (97)	Cure 83/96 (86)	Ceftriaxone in all courses
Gentamicin q24h[44]	Cure 86/90 (96)	Bacterial eradication 58/60 (97)	None
Gentamicin q8h[44]	Cure 87/89 (98)	Bacterial eradication 58/59 (98)	None
Gentamicin q24h[45]	Cure 23/26 (88)	Cure 10/10 (100)	Ampicillin 12/26 (46) Metronidazole 16/26 (62)
Gentamicin q8h[45]	Cure 22/24 (91)	Cure 12/13 (92)	Ampicillin 10/24 (42) Metronidazole 10/24 (42)
Amikacin[52]	Cure 46/56 (82) Improvement 9/56 (16)	Bacterial eradication 49/55 (89)	Various antibiotics 49/56 (86)
Amikacin q24h[46]	Cure 12/13 (92)	Not evaluated	Piperacillin in all courses
Amikacin q12h[46]	Cure 9/10 (90)	Not evaluated	Piperacillin in all courses
Gentamicin q24h[47]	Cure 20/22 (91)	Not evaluated	Piperacillin in all courses
Gentamicin q8h[47]	Cure 27/30 (90)	Not evaluated	Piperacillin in all courses
Gentamicin[49]	86/113 (76) required no change of first-line therapy	Not evaluated	Ceftriaxone in all courses
Amikacin[51]	Cure 25/25 (100)	Cure 25/25 (100)	Various antibiotics 8/25 (32)
Tobramycin q24h[48]	Improvement 12/12 (100)	Not evaluated	Ceftazidime in all courses
Tobramycin q8h[48]	Improvement 10/10 (100)	Not evaluated	Ceftazidime in all courses

Toxicity in Children

Nephrotoxicity

Eleven studies assessed nephrotoxicity associated with ODD aminoglycoside therapy in children (Table 3).[44, 45, 47–55] Most of them defined nephrotoxicity as a percentage increase in serum creatinine concentration over baseline or a percentage decrease in creatinine clearance from baseline. In addition to creatinine clearance monitoring, 24-hour proteinuria, lysozymuria, and

B2 microglobulinuria were measured to determine nephrotoxicity.[48] One study did not report any nephrotoxicity but did not detail methods used to assess the complication.[52]

All of the studies reported that minimal or no nephrotoxicity occurred regardless of dosing regimen. Overall, nephrotoxicity was evaluated in 140 (79%) of 177 and 530 (75%) of 707 traditional and ODD treatment courses, respectively. It was not reported in any of the 140 courses of traditional therapy but was reported in 4 (0.75%) of 530 ODD treatment courses. One trial defined nephrotoxicity as a rise in serum creatinine of more than 50% over baseline.[49] The mean serum creatinine concentration for the entire study group remained unchanged after gentamicin treatment. However, two episodes met criteria for nephrotoxicity. In both children the Hartford nomogram8 was used to change the gentamicin dosing interval to 36 hours. Serum creatinine returned to baseline within 14 days after discontinuation of treatment in both children.[49] One case of nephrotoxicity was reported after ODD amikacin.[51] Serum creatinine rose 93% in a 15-month-old child with pyelonephritis and leukemia; follow-up evaluation was not performed. Nephrotoxicity occurred on day 14 of amikacin therapy in a child who was concomitantly receiving cyclosporine.[53] The disorder resolved with discontinuation of amikacin and adjustment of cyclosporine dosage.[51]

Table 3. Nephrotoxicity with Once-Daily Aminoglycoside Dosing in Children

Drug	Nephrotoxicity Evaluation Method	No. of Nephrotoxic Patients/Total Patients (%)
Gentamicin q24h[54]	Serial creatinine clearance	0/31
Gentamicin q8h[54]		0/17
Amikacin q24h[50]	Serum creatinine concentration	0/155 courses
Tobramycin q24h[55]	Daily serum creatinine concentration	0/7
Gentamicin q24h[44]	Serum creatinine concentration	0/64
Gentamicin q8h[44]		0/52
Gentamicin q24h[45]	Serum creatinine concentration	0/32
Gentamicin q8h[45]		0/31
Amikacin q24h[52]	Not reported	0/56
Gentamicin q24h[47]	Serum creatinine concentration	0/22
Gentamicin q8h[47]		0/30
Gentamicin q24h[49]	Serum creatinine concentration	2/113 (1.8) courses
Amikacin q24h[51]	Serum creatinine concentration	1/25 (4)
Tobramycin q24h[48]	Renal indexes days 1 and 14 of treatment	0/12
Tobramycin q8h[48]		0/10
Amikacin q24h[53]	Creatinine clearance	1/13 (7.7)

Ototoxicity

Eight studies used audiologic assessments at baseline and at a determined follow-up point after aminoglycoside treatment to evaluate ototoxicity (Table 4).[44, 45, 48, 49, 52–55] Overall, 57% (171/300) and 56% (83/147) of patients receiving ODD and traditionally dosed aminoglycosides, respectively, were assessed with an audiometric examination. Four studies reported at least one

episode of ototoxicity, with a frequency of 8–14%.[45, 49, 53, 55] In one study the side effect was not clinically significant55; the other three studies did not comment on clinical significance.[45, 49, 53] The overall frequency of ototoxicity in the eight studies was 3.5% (9/254), with it occurring in 4.1% (7/171) and 2.4% (2/83) of patients treated with ODD and traditional regimen, respectively.

Pharmacokinetic Analysis

Six of 13 studies measuring aminoglycoside serum concentrations compared ODD with traditional dosing.[44–48, 54] Peak concentrations were measured in each study 30 minutes after a 30-minute infusion.[44–48, 54] As expected, they were significantly higher and trough concentrations lower with ODD than with traditional dosing. Patients with neutropenic fever and suspected bacterial infection were randomized to receive gentamicin 5 mg/kg/day in one or three doses.[47] A serum peak concentration greater than 10 μg/ml was achieved in 77% and 44% of the patients, respectively. In surgical patients, gentamicin 7.5 mg/kg/day administered as one dose was compared with three divided doses.54 Average peak serum concentrations were 20.4 and 7.2 μg/ml ($p<0.0001$) and trough concentrations 0.29 and 0.69 μg/ml ($p<0.0001$), respectively. In febrile and neutropenic children with cancer and suspected bacteremia randomized to receive amikacin 20 mg/kg/day in one or two doses, mean peak concentrations were 42.6 and 19.1 μg/ml and trough concentrations 0.85 and 0.18 μg/ml, respectively.[46]

Table 4. Ototoxicity with Once-Daily Aminoglycoside Dosing in Children

Drug	Ototoxicity Evaluation Method	No. of Patients with Ototoxicity/ Total Patients (%)
Gentamicin q24h[54]	Audiology assessments at baseline and at completion of therapy	0/31
Gentamicin q8h[54]		0/17
Tobramycin q24h[55]	Audiometry before and at end of treatment	1/7 (14)
Gentamicin q24h[44]	Audiologic assessments at baseline and within 2 mo of discharge	0/39 after treatment
Gentamicin q8h[44]		0/33 after treatment
Gentamicin q24h[45]	Audiologic assessments at baseline and within 7 days of treatment end	2/26 (7.7)
Gentamicin q8h[45]		2/24 (8.3)
Amikacin q24h[52]	Audiometry before and after therapy	0/25
Gentamicin q24h[49]	Audiometry after a minimum of 2 wks off treatment	3/30 (10)
Tobramycin q24h[48]	Audiograms days 1 and 14 of therapy	0/10
Tobramycin q8h[48]		0/9
Amikacin q24h[53]	Audiometry at baseline and within 1 wk after discontinuation of treatment	1/10 (10)

Similarly high peaks and low troughs were observed in the seven studies evaluating only an ODD regimen.[49–53, 55, 56] Two groups did not report the peak concentration as that obtained 30 minutes after a 30 minute infusion.[52, 55] One group reported the values measured 1 hour after the start of a 15- or 30-minute infusion.[52] The other reported concentrations 1 hour after the dose.[55] Other investigators evaluated serum gentamicin concentrations measured 6–14 hours after the first dose and every 5 days thereafter.[49] The Hartford nomogram8 was used to adjust gentamicin dosing intervals. Eight hours after the start of the infusion, all concentrations were below the 24-hour line on the nomogram. This is not surprising, given increased aminoglycoside clearance in children compared with adults. In a similar study, children with fever and neutropenia undergoing bone marrow transplantation were treated with a single daily dose of amikacin 20

mg/kg plus ceftazidime.53 Amikacin serum concentrations 6, 12, and 24 hours after infusion were undetectable (< 3 μg/ml) on days 1 and 4 of therapy.

Discussion

The published literature for ODD of aminoglycosides for infants and children is not as extensive as is that for adults. Results from studies in approximately 700 nonneonatal pediatric patients appear to parallel those in adult studies. However, efficacy was evaluated in only approximately 450 of the 700 patients receiving an ODD regimen. The other patients are accounted for in studies that performed only pharmacokinetic analyses.

In pediatric studies comparing ODD and traditional aminoglycoside regimens, clinical and microbiologic efficacy were similar between groups.[44–47] Peak serum concentrations were significantly higher with ODD than with traditional regimens. It is difficult to determine if bactericidal activity was truly greater with ODD since none of these studies reported MIC values of infecting organisms.[44–47] It cannot be concluded that ODD maximized clinical efficacy because of similar results in both treatment groups.

Dosing regimens and patient populations must be reviewed before extrapolating clinical efficacy results of comparative studies into pediatric practice. An age-dependent dosing strategy for urinary tract infections was used in one study.44 Starting dosages of gentamicin were 4.5–7.5 mg/kg/day, and adjustments were made in the traditionally dosed group to keep the peak serum concentration above 5 μg/ml. This traditional dosing regimen may be adequate for most urinary tract infections, as was illustrated in these children with clinical cure rates of 90–98%; however, the same dosages divided into three doses may not be sufficient for patients with more severe infections.

Efficacy rates were similar (88–91%) in patients with suspected gram-negative bacterial infections.45 The urinary tract (46%) and laparotomy sites (52%) were primary sources of infection in this patient population. Therapy was begun with gentamicin 4.5 mg/kg/day; again, this dosage was adequate for the infections in these patients but may not be sufficient for many infectious processes in children such as gramnegative sepsis, bacteremia, and nosocomial infections. It is difficult to determine whether a more typical dosing approach (e.g., 7.5–9 mg/kg/day) would have resulted in even greater efficacy in traditionally dosed patients in the above two studies.

Failure rates were similar between ODD and traditional dosing regimens in patients with neutropenic fever.[47] Patients failing to respond to initial therapy were changed from gentamicin to amikacin. No deaths were reported. Gentamicin 5 mg/kg/day was the dosage in the traditional arm rather than the more common starting dosage of 7.5 mg/kg/day. All patients received piperacillin in addition to gentamicin, which was general practice when an aminoglycoside was administered for neutropenic fever. Once-daily and twice-daily amikacin, both 20 mg/kg/day, yielded similar efficacy.[46] A more appropriate traditional dosing interval would have been every 8 hours rather than every 12 hours, given that the average age of patients in that treatment group was 5 years. Patients who failed to respond to amikacin were changed to ceftazidime. What is important to note in these two studies is that regardless of dosing regimen and concurrent

antibiotics, treatment failures were similar between ODD and traditionally dosed aminoglycosides. In addition, it is difficult to detect whether ODD offered a change in true efficacy given that the traditional dose was not the most appropriate and that all children received an additional broad- spectrum antibiotic.

Of nine studies that evaluated clinical and/or microbiologic efficacy, all but one administered concomitant antibiotics. Patients with uncomplicated urinary tract infections received monotherapy with gentamicin.[44] The other eight studies administered a variety of cephalosporins, penicillins, and carbapenems as well as agents such as clindamycin and metronidazole.[45–52] These additional antibiotics make it difficult to assess accurately the efficacy of extended-interval aminoglycoside monotherapy. Administering two or more antimicrobials for certain pediatric infections is consistent with current clinical practice.

Of concern is the 36% failure rate for gramnegative infections in one trial.[50] *Pseudomonas* sp accounted for 32% of these infections.50 Febrile patients with cancer with or without neutropenia received a combination of amikacin and ceftriaxone. Since ceftriaxone does not have reliable, if any, activity against *Pseudomonas* sp, an antipseudomonal β-lactam antibiotic would have been a more appropriate choice.

There are few comparative data to assess efficacy of ODD versus traditional dosing in children, and available studies showed similar results. It is also difficult to extrapolate results of comparative studies to current practice because infections in the study populations did not represent the full range of pediatric infections encountered in clinical practice. Dosages in traditional regimens in a number of these trials were lower than recommended in common pediatric references.[27] A number of pediatric studies evaluated only ODD and showed it to be both clinically and microbiologically effective. Whereas it is difficult to state decisively that ODD maximizes clinical and microbiologic efficacy based on the nine studies that determined efficacy, it can be concluded that ODD does seem to be an equally effective alternative to traditionally dosed aminoglycosides.

One premise that ODD is based on is that nephrotoxicity is related to increased trough serum concentrations as well as duration of therapy and accumulation of drug. Therefore, an extended interval should result in lower or undetectable trough concentrations that could lead to less renal toxicity. All but one study evaluating nephrotoxicity used either an increase in serum creatinine or a decrease in creatinine clearance as safety end points, which are appropriate and common methods of evaluating potential nephrotoxicity in clinical practice. The remaining study reported no nephrotoxicity but did not discuss methods used to assess renal function.[52] When looking at all studies of nephrotoxicity, no patients treated with a traditional aminoglycoside regimen met criteria for the disorder. The adverse effect was reported in four patients treated with ODD regimens.[49, 51, 53] Studies comparing a traditional with a ODD regimen did not report nephrotoxicity in either group. Therefore, the theory that ODD produces less nephrotoxicity due to lower trough concentrations is not substantiated in pediatric studies. This may be due in part to increased clearance of aminoglycosides and to how well the drugs are tolerated in children.

A prominent deficiency of studies evaluating ototoxicity was the number of patients evaluated. The overall ototoxicity rate was 3.5% in these studies, but only 57% and 56% of patients

receiving ODD and traditionally dosed aminoglycosides were assessed at baseline and after discontinuation of therapy. There is a substantial difference in the frequency of ototoxicity when comparing the two regimens. The disorder occurred in 4.1% versus 2.4% of patients treated with ODD versus traditional dosing, respectively.[44, 45, 48, 49, 52–55] That equates to a 71% difference between regimens when results of the eight studies are combined. Pediatric studies that assessed nephrotoxicity showed minimal difference between regimens, but the same cannot be said for ototoxicity. The study samples were relatively small, and not all patients had audiologic assessment, but the difference in frequency of ototoxicity is of concern. More data are required to make a sound conclusion regarding the effect of ODD on ototoxicity.

Pharmacoeconomic effects may be associated with ODD. Potential cost savings may be realized in personnel time, drug and supply costs, preparation time, and serum concentration assays. This regimen also offers a more convenient method for administration of antibiotics at home. A hospital savings of $178.23/patient, or 66% reduction, was calculated when ODD regimens replaced standard regimens.[57] The calculations took into account nursing and pharmacy staff time, drug and supply costs, monitoring of serum concentrations, and toxicity management, but not pharmacist time for monitoring patients. Another group estimated that ODD would result in an approximate saving of $14.64/patient/day in nursing charges and a cost avoidance of $64.50/patient each time drug concentrations were measured.[54]

Once-daily aminoglycoside dosing for children is an alternative, but not standard practice, in many hospitals. Some concerns are lack of pediatric data, increased aminoglycoside clearance in children, lack of standard dosing and/or dosing nomograms, and efficacy and safety. Two of the greatest concerns center on the efficacy of ODD as it relates to more rapid drug clearance in children and lack of a standard and accepted dosing approach. Daily doses in pediatric studies were 4.5–15 mg/kg for gentamicin and tobramycin and 15–20 mg/kg for amikacin. It is important to note that some of these dosages may be lower than what is commonly prescribed in traditional regimens. Thus a standard dosage for ODD cannot be extrapolated from these studies.

Children with normal renal function eliminate aminoglycosides more rapidly than adults. In many instances it is feasible for a child receiving ODD to have a serum concentration below detectable limits for a significant portion of the dosing interval. Depending on the patient's drug clearance and other patient characteristics, this time below detectable limits, or time below MIC, could range from a few hours to 12–16 hours. Whereas aminoglycoside antibiotics do benefit from a PAE, the duration of the PAE in animal and in vitro human models ranged from 1–8 and 1–2 hours, respectively.30–32 In a mouse model bacteria regrew and reached initial infection levels approximately 6 hours after a single high dose of netilmicin, even in the presence of a PAE.[24]

Is efficacy being compromised when the serum concentration is allowed to remain undetectable for a significant period of time, given this indication of bacterial regrowth? Results of limited pediatric studies indicate that efficacy was not compromised in most patients receiving ODD. As mentioned, these comparisons were compromised in some cases by inappropriate dosages in traditional regimens. In addition, aminoglycosides rarely are given for monotherapy for suspected or confirmed gram-negative bacteremia; in such children they typically are combined with a β-lactam antibiotic.

One response to the concern of compromised efficacy when serum concentrations remain undetectable for long periods of time could be to shorten the dosing interval according to a dosing nomogram similar to the Hartford nomogram. How long the serum concentration can remain below detectable limits before a change in dosing interval is necessary is not known and must be determined before a nomogram can be developed and tested. Another option would be for clinicians to revert to traditional dosing. This would seem logical when serum concentrations are undetectable for prolonged durations or when patients respond poorly. However, such a change could make achieving preferred peak:MIC ratios difficult in patients with intermediately susceptible bacterial infections.

Conclusion

Although data for aminoglycoside ODD in children include only approximately 700 patients, most results indicate that this method is as effective as traditional dosing. More safety data are required in children, however, since only 75% and 56% of patients receiving ODD had an adequate nephrotoxicity or ototoxicity assessment, respectively. It is important to consider study limitations when evaluating the overall efficacy and safety of ODD in children. The comparative studies are limited by small samples, use of traditional dosages that are lower than those in current practice, lack of routine assessment of baseline and posttreatment auditory and vestibular function, and limited number of patients with documented gramnegative bacteremia.

Once-daily aminoglycoside dosing appears to be appropriate and effective as monotherapy for uncomplicated urinary tract infections and for treatment or prevention of surgical infections. It should be considered when the drug is administered with an appropriate β-lactam antibiotic (with or without anaerobic coverage). In addition, ODD appears to be appropriate in combination with an antipseudomonal antibiotic for fever and neutropenia. Given the clinical practice of administering concomitant antibiotics with aminoglycosides for gram-negative bacteremia in children, ODD could be an acceptable alternative in this population. However, additional studies must be performed in patients with gram-negative bacteremia, sepsis, and/or septic shock before it can be recommended consistently. This regimen appears appropriate in combination with an antipseudomonal antibiotic for patients with cystic fibrosis. However, these patients may require higher dosages to achieve a peak: MIC ratio of 8–10:1 based on a higher distribution volume and the potential for intermediately susceptible or resistant microorganisms. Once daily dosing should not be used in pediatric burn patients, given altered pharmacokinetics of aminoglycosides and lack of data of ODD in this population. In addition, it should not be used in children with abnormal renal function.

Based on dosages in available studies and on population pharmacokinetic parameters at the authors' practice sites, gentamicin or tobramycin 7–8 mg/kg every 24 hours is recommended as initial therapy in children with conditions other than cystic fibrosis. Based on population pharmacokinetics at our practice sites, this dosage is estimated to achieve a peak concentration of 20 μg/ml and trough concentrations of less than 1 μg/ml. A goal peak concentration of 20 μg/ml was chosen so that a peak:MIC ratio of 10:1 would be attained for an organism with an MIC of 2 μg/ml to gentamicin or tobramycin. A recommendation for amikacin ODD cannot be made at this time.

Since dosing nomograms are not available for use with children, serum concentrations should be monitored. For patients receiving ODD with an anticipated duration of treatment less than 72 hours, a concentration before the second dose should be measured to ensure that the trough concentration is less than 1 μg/ml. For patients receiving ODD with an anticipated duration of treatment greater than 72 hours, two options are available. One is to measure a concentration before the second dose as above. Also, a peak concentration obtained 30 minutes after the end of the infusion of the second dose should be drawn to ensure a peak: MIC ratio of 8–10:1. The second option is to measure a peak concentration 30 minutes after the end of the infusion of the first dose to ensure that it is adequate. A midinterval serum concentration 8–10 hours after the first dose should be measured to extrapolate a trough concentration. For patients without a positive culture and therefore no MIC data, the peak concentration should be maintained between 16 and 20 μg/ml.

Safety of aminoglycoside therapy should be monitored for both ODD and traditionally dosed regimens. Serum creatinine should be monitored at baseline and frequently thereafter for nephrotoxicity. In addition, urine output is a good clinical indicator of renal function and should be monitored daily. Consideration should be given to changing the dose and/or interval, or measuring serum concentrations if there is a clinically significant increase in serum creatinine or decrease in urine output from baseline. Ideally, audiometric assessments would be completed before starting and at some point during therapy. However, this is not always clinically feasible given the frequency with which these drugs are administered to children. Close monitoring for nephrotoxicity and ototoxicity is necessary in patients with cystic fibrosis due to the number of aminoglycoside treatment courses they receive. Dose-finding studies with a focus on nomogram development as well as safety and efficacy assessment should be performed in large samples of children to answer some of the clinically relevant and currently unanswered questions.

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