Extended-interval Aminoglycoside Dosing in Pediatrics

Alice M. Jenh, PharmD, BCPS,* Pranita D. Tamma, MD,† and Aaron M. Milstone, MD, MHS‡

Key Words: aminoglycosides, extended-interval dosing, pediatrics

(Pediatr Infect Dis J 2011;30: 338–339)

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minoglycosides (AGs) are often used in combination with β-lactam antibiotics for the treatment of serious Gram-negative infections. Traditionally, AGs have been dosed multiple times a day. Over the past decade, extended-interval dosing has been evaluated as a method of improving the efficacy and safety of AGs. Extended-interval aminoglycoside dosing (EIAD) generally consists of administering the total daily dose as one dose, usually every 24 hours. EIAD optimizes drug efficacy without compromising safety. This article reviews the rationale for EIAD, as well as safety and efficacy of EIAD in pediatric patients.

RATIONALE FOR EIAD

Concentration-dependent Bactericidal Activity

AGs are concentration-dependent killers. Optimizing the ratio of peak serum concentration over the minimum inhibitory concentration (peak/MIC) maximizes AGs bactericidal activity.1 Clinical data in adults demonstrate that peak AG concentrations are strongly associated with therapeutic efficacy, and a goal peak/MIC ratio of 8–10 should be targeted for maximal bacterial killing.2 Higher mg/kg doses can be used with EIAD to maximize the peak/MIC ratio (Fig. 1).

Postantibiotic Effect

Evidence from in vitro and animal studies indicate that AGs exhibit a postantibiotic effect defined as the suppression of bacterial growth after the serum drug concentration has dropped below the MIC.3 Increased initial AG concentration has been correlated with longer duration of the postantibiotic effect. With EIAD, there is a drug-free period at the end of the dosing interval, during which AG concentrations fall below the MIC for a period of time, but drug efficacy is not compromised because the postantibiotic effect prevents bacterial regrowth.

SAFETY OF EIAD

Nephrotoxicity

AG-induced nephrotoxicity results from the accumulation of drug within the kidneys. Elevated AG trough concentrations are associated with the development of nephrotoxicity, and the frequency of dosing appears to be a risk factor. Human studies have shown that AGs dosed multiple times a day results in greater accumulation of the AG within the renal cortex than single daily injections.4 In a prospective randomized trial of adult patients, EIAD achieved lower trough serum concentrations and resulted in a significantly lower incidence of nephrotoxicity when compared with traditional dosing.5 A meta-analysis of pediatric randomized clinical trials did not detect significant differences between EIAD and traditional dosing in terms of increases in serum creatinine or decreases in creatinine clearance; however, a difference would be more difficult to detect due to the generally lower incidence of nephrotoxicity in children when compared with adults (<2% vs. 5%–8%).6

Ototoxicity

The mechanism of AG ototoxicity is less well understood and manifests as both cochlear and vestibular dysfunction. The reported incidence varies widely due to inconsistent definitions and methods of assessing ototoxicity. Animal data suggest that ototoxicity is related to penetration of AGs into the inner ear tissues.7 Higher inner ear tissue concentrations are observed with continuous infusions of AGs compared with single daily injections. Clearance of AG from the inner ear tissues is extremely slow, resulting in prolonged AG exposure and subsequent damage. Unlike AG-induced nephrotoxicity, a clear correlation between AG-induced ototoxicity and serum concentrations has not been demonstrated. It has been suggested that ototoxicity may correlate with cumulative total exposure to AGs through prolonged durations or repeated courses of therapy.8 Theoretically, EIAD might result in less accumulation of AG in the inner ear tissues, reducing ototoxicity; however, this has not been demonstrated in clinical trials to date.

In a meta-analysis of pediatric studies, there were no differences in auditory toxicity or vestibular toxicity between EIAD and traditional dosing, which is consistent with adult studies.9 However, due to the limited formal testing in these trials, subtle deficits might have gone undetected.

Efficacy of EIAD

A study in adults demonstrated that EIAD of gentamicin and tobramycin resulted in comparable response rates, significantly less nephrotoxicity, and low rates of ototoxicity when compared with a historical control group receiving traditional dosing.9 Multiple prospective comparative trials in adult and pediatric patients with various infections (including serious Gram-negative infections, cystic fibrosis (CF) exacerbations, fever with neutropenia, and urinary tract infections) have been completed. Meta-analyses of these studies have demonstrated that EIAD is equivalent or superior to traditional dosing in terms of clinical efficacy and nephrotoxicity, and not significantly different compared with traditional dosing in terms of ototoxicity and mortality rates.

A meta-analysis of 24 randomized clinical trials evaluating the use of EIAD versus traditional dosing in pediatric populations found no statistically significant differences in the proportion of clinical or microbiological failure between EIAD and traditional dosing arms (23/501 [5%] of cases for EIAD versus 34/494 [7%] of cases for traditional dosing).9 However, there were fewer combined clinical or microbiologic failures with EIAD versus traditional dosing in the amikacin clinical trials (RR: 0.41 [95% CI: 0.22–0.77]). This finding was largely influenced by one clinical trial that randomized critically ill adult patients with documented Gram-negative infections to amikacin once versus twice daily, both in combination with β-lactam antibiotics.10 Overall clinical and microbiologic cure rates were significantly higher in the once daily amikacin group versus the twice daily group. In patients with Pseudomonas spp. infections, higher failure rates were noted in patients treated with twice daily amikacin versus once daily.

Due to the enhanced clearance of AGs, many children will have undetectable AG concentrations for a significant portion
of a 24-hour dosing interval with EIAD that is potentially beyond the duration of the postantibiotic effect. It is unknown whether prolonged periods of undetectable AG concentrations compromise efficacy or allow for bacteria to regrow; however, clinical trial data in pediatric patients do not support these concerns. A small randomized trial in adult CF patients demonstrated significant increases in the MICs of Pseudomonas spp. at the end of therapy with EIAD of tobramycin compared with traditional dosing. Increases in MICs should be monitored for with EIAD, and further studies are needed to confirm these findings.

APPLICATION OF EIAD IN PEDIATRICS

Although EIAD has become widely used in many adult settings, use in pediatric populations has lagged behind. Reported concerns regarding EIAD in pediatrics include lack of consensus on target populations, appropriate dosing, ideal interval, and therapeutic drug monitoring. In our institution, EIAD is primarily used in pediatric CF patients and oncology patients exposed to prolong and multiple courses of AGs. In non-CF pediatric patients, we have used dosages of gentamicin or tobramycin at 7 to 8 mg/kg once daily and amikacin 15 to 20 mg/kg once daily. In pediatric CF patients, we have used dosages of tobramycin 10 to 12 mg/kg once daily and amikacin 30 to 35 mg/kg once daily. For patients with a known organism and MICs, we obtain a peak drawn 30 minutes after the end of the infusion to target a peak/MIC ratio of at least 8–10, and a trough before the next dose or a midinterval level (~8–12 hours after the first dose) to extrapolate a trough. For patients without a known organism, a trough prior to the next dose is obtained to document clearance. In pediatric populations other than CF and oncology, we determine EIAD usage on a case by case basis. As EIAD has not been evaluated in patients with impaired renal function, or in certain patient populations (eg, extensive burns, obese, or patients with ascites) in which the volume of distribution for AGs is significantly altered, we would not recommend EIAD in these patients. Additionally, we would not recommend EIAD for certain severe infections including meningitis, osteomyelitis, persistent bacteremia, and Enterococcus spp. endocarditis.

CONCLUSION

Although the clinical experience with EIAD in children is limited, available evidence in pediatric patients suggest that EIAD is equally efficacious compared with traditional dosing in select patient populations, and no differences in toxicity have been observed. Additional studies in pediatric patients with Gram-negative sepsis, bacteremia, and pneumonia are needed before EIAD can be routinely used. Close monitoring of nephrotoxicity and ototoxicity is necessary in all patients treated with AGs regardless of the dosing interval.

REFERENCES