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Extended-Interval Dosing of Aminoglycosides in Pediatrics: A Narrative Review

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Aminoglycosides (AGs) are frequently used in pediatric settings, especially for empiric treatment of early-onset neonatal sepsis. Although AGs are used for several decades, the optimum method of administration and their dosing schemes needs more clarification. The risks of ototoxicity and nephrotoxicity, two main toxicities associated with AGs, have been contributed to the peak and trough plasma levels, respectively. One approach to decrease these potential toxicities of AGs is to administer higher doses with a prolonged interval, named extended-interval dosing (EID). Post-antibiotic effect (PAE) and concentration-dependent killing of AGs provide rational basis for the efficacy of EID. PAE refers to the extended bactericidal activity of AGs against many Gram-negative organisms after the drug was removed by metabolism. One concern is that the higher initial peak concentration with EID may be accompanied with more toxicities, especially ototoxicity. It was demonstrated that due to saturation of binding site of AGs in renal and cochlear tissues, transiently higher concentration of AGs does not cause additional nephrotoxicity or ototoxicity. Experience and clinical evidence regarding EID in pediatrics is suboptimal. In this review, we presented the rational and studies focusing on EID in pediatric setting. The overall finding of trials is that in pediatric setting, EID is a safe and effective dosing method. The risk of serum drug concentration outside the therapeutic range is lower in neonates treated with EID, leading to less need of therapeutic drug monitoring (TDM) with EID. Moreover, there are evidences supporting lower chance of bacterial resistance with EID compared with traditional dosing approach.

Keywords: Aminoglycosides; Neonates; Drug Dosage

1. Context

Aminoglycosides (AGs) as a group of bactericidal antibacterial agents are frequently used in treating patients with different infections. These agents have good antibacterial activity against some Gram-positive and Gram-negative bacteria, especially multidrug resistant strains such as *Enterococcus* spp., *Acinetobacter* spp., and *Pseudomonas* spp. AGs are frequently prescribed empirically as a component of antibacterial regimen in most cases with severe illness or complicated disease, nosocomial infections and infection in immunocompromised hosts (1, 2). Aminoglycosides (AGs) are frequently used in pediatric settings, especially for empiric treatment of bacterial infections in early-onset neonatal sepsis (3, 4). Two main well-known adverse effects of aminoglycosides detected since 1970 are nephrotoxicity and ototoxicity. The risk of ototoxicity and nephrotoxicity has been attributed to the peak (plasma concentration measured after the dose) and trough (plasma concentration measured before the next dose) levels of AGs, respectively (5). To prevent or decrease the risk of oto-nephro-toxicities of AGs, serial monitoring of sera concentration of AGs is required. This approach (frequent parenteral administration and serial monitoring) is not feasible in most places, especially developing countries. To solve this problem, administration of higher dose of antibiotics with longer interval was investigated.

Routinely, in adult patients with normal renal function, aminoglycosides (e.g., gentamycin and tobramycin) are administered as 1 to 3 mg/kg intravenously every eight hours. The dose should be adjusted in patients with decreased renal function, either lowering the dose, or increasing the interval of AG. One approach to decrease these potential toxicities of AGs is to administer higher doses with a prolonged interval (e.g., 7 mg/kg each 24 hours in adult population), named extended-interval dosing (EID) of AGs (1). EID of AGs is different from dose adjustment in patients with decreased renal function who receive usual doses (i.e. 1 - 3 mg/kg) at 24-hour interval. Although AGs are used for several decades, the optimum method of administration and their dosing schemes needs more clarification. Our previous studies showed that both in our pediatric (6) and adult settings (7, 8), physicians almost always practice the traditional dosing of AG. In addition, experience and clinical evidence regarding this issue in pediatrics is suboptimal. The aim of this review was to discuss the rational, advan-

tages and issues surrounding EID of AGs in the pediatric setting.

2. Evidence Acquisition

A narrative review was written to discuss the rational, advantages and issues surrounding Aminoglycosides in the pediatric setting and all the cited-articles were extracted from PubMed/Medline database. Fifty-six articles comparing single-daily dose and multiple-daily dose of AG in preterm and term neonates and children were collected in the initial step of searching and thirty-two studies that were more relevant to the review topic were included in the final manuscript. The qualitative results extracted from the reviewed articles are presented here.

3. Results

3.1. Rational of Single Daily Dosing

AGs have two pharmacodynamic characteristics that provide basis for the efficacy of EID including post-antibiotic effect (PAE) and concentration-dependent killing. PAE refers to the extended bactericidal activity of AGs against many Gram-negative organisms after the drug was removed by metabolism. The duration of PAE is three hours (ranged 1 to 7.5 hours). On the other hand, there is a direct association between the concentration and killing effect of AGs, meaning that higher concentrations are associated with better killing of microorganisms. One concern is that the higher initial peak concentration with EID may be accompanied with more toxicities, especially ototoxicity. It was demonstrated that due to saturation of binding site of AGs in renal and cochlear tissues, transiently higher concentration of AGs does not cause additional nephrotoxicity or ototoxicity (9). Increasing the dose to improve the peak concentration for better killing would be accompanied with higher trough levels if the interval would not be extended over traditionally eight hours (10). EID provides the optimal (e.g., higher) peak concentration, while with an extended interval, there would be enough time for the body to metabolize the drug to achieve safe trough levels (e.g. less than 1 - 2 mcg/mL for gentamycin and tobramycin). The PAE would attenuate the concern regarding lack of efficacy with increasing the intervals. Indeed, EID was proposed to both improve the efficacy and decrease the toxicity profile of AGs (11). EID of AGs may reduce the risk of nephrotoxicity, because the trough levels are usually attributed to the nephrotoxicity (12). In addition to decreased nephrotoxicity, several other benefits were proposed including ease of administration, less need to serum concentration monitoring and less cost related to administration and monitoring (13). Considering both pharmacokinetic (PK) and pharmacodynamic (PD) information, Li and Nekka (14) confirmed the superiority of EID of aminoglycosides compared to traditional dosing schedule. In several clinical conditions, especially critically ill patients, expansion of the extracellular space may lead to a lower than desirable peak concentration with the usual loading dosage. Another benefit of EID is to decrease the chance of bacterial resistance. With extending the interval, complete clearance of the drug would happen before the subsequent doses and less exposure of microorganism decreases the rate of resistance (1).

3.2. Review of Trials

The effectiveness of EID was demonstrated in animal models (15). For example, in experimental *Escherichia coli* meningitis model, it has been demonstrated that EID was at least as affective as traditional dosing method in reducing the bacterial counts in cerebrospinal fluid. In the last decade, a few trials have been conducted to evaluate the efficacy and safety of EID in pediatric and neonatal infections.

In a prospective randomized controlled trial, Agarwal et al. (13) demonstrated that extended interval dosing of gentamycin 4 mg/kg was associated with higher peak concentrations and a safer trough concentrations in all infants in their study. In addition, the safety advantage of EID of gentamycin may eliminate the need of therapeutic drug monitoring in infants with a normal renal function. Peak SGC between 5 and 12 mcg/mL and trough SGC of < 2 mcg/mL were considered therapeutic levels (13). In a prospective randomized study on Thai neonates with gestational age ≥ 34 weeks or body weight ≥ 2000 grams, traditional gentamycin doses 2.5 mg/kg every 12 hours was compared with 5 mg/kg every 24 hours. EID was associated with higher peak and lower trough concentrations. It was interesting that 68% of patients in traditional dosing and 22% in EID group still had a trough level more than 2 mcg/mL. it may imply that extending the interval to 24 hours may not completely guarantee a safe trough level (16). Very recently in a relatively large study (113 neonates with different gestational ages) conducted in a Malaysian hospital, Low et al. (17) confirmed that extended-interval gentamycin is associated with improved therapeutic concentration (82.3%) in both term and premature neonates. A total of 112 patients (99.1%) achieved desired therapeutic trough concentration of < 2 mg/L, a finding that emphasizes the safety of EID of AGs in this population (17).

In other studies, favorite results obtained in preterm neonates (≤ 28 weeks) admitted to NICU. Extended-interval dosing (EID) of gentamycin 5 mg/kg/day was compared with 2.5 mg/kg/day divided TID as traditional interval dosing. After the first dose of 5 mg/kg, the following intervals were adjusted according to plasma concentration drawn at 22 hours after the first dose. Compared to the TID group, need for dose adjustment was lower in EID group and also the peak levels were higher in EID group. It has been suggested that EID regimen from the first day of life accompanied with a single level 22 hours after the first dose for dosing interval was associated with more

desired therapeutic peak and trough concentrations compared to a TID regimen (18).

In another study in preterm infants, amikacin was used with a 10 mg/kg loading dose followed by 7.5 mg/kg/day in the first week of life. After the first week of life, the loading dose and maintenance dose increased to 17 mg/kg and 15 mg/kg, respectively. The favorite peak and trough levels for amikacin were >35 micromol/L and < 8.5 micromol/L, respectively. With this dosage of amikacin, except extremely low weight patients (< 700 g) and and/or with a gestational age of ≤ 24 weeks, therapeutic peak and trough concentrations were achieved (19). Another study revealed that once-daily dosing results in peak and trough levels that are in safe and therapeutic range in all term neonates. In low birth weight neonates (gestational age < 37 weeks or weight < 2500 g and > 1500 grams), this regimen resulted in peak and trough levels as traditional dosing. In patients with very low birth weight (weight < 1500 g), the mean initial trough levels were higher than the control group (20). In addition to very low weight neonates, for some other specific group of neonates, it may be necessary to extend the interval of AGs for more than 24 hours. In a recent study of Frymoyer et al. (21), which included neonates with hypoxic ischemic encephalopathy, the extending interval of gentamycin 5 mg/kg from 24 hours to 36 hours was associated with improvement on achieving target trough concentration and a favorable peak concentration. The usefulness of EID of AGs for safety and efficacy was demonstrated in preterm infants (22). In most clinical trials, equal daily AG doses as EID (dosage interval typically 24 hours in term and 36 - 48 hours in immature neonates) compared with traditional dosing (dosage interval typically 8 - 12 hours in term and 12 - 24 hours in immature neonates). The overall finding is that EID is safe and effective and the risk of serum drug concentration outside therapeutic range is lower in neonates treated with EID (13, 16, 20, 22-24). In addition to preterm and term infants, the effectiveness of EID of AGs was documented in children. Once-daily dosing of gentamycin was safe and efficacious with a more favorable clinical response (89% versus 76%) and more favorable peak concentrations (100% in once-daily dosing versus 87% in multiple-daily dosing). Moreover, undesirable range of trough concentrations was 0% and 17% in once-daily dosing and multiple daily dosing, respectively (25). Similar results were reported in febrile neutropenic children who received stem cell transplantation. Single-daily dose of tobramycin was associated with better efficacy and less nephrotoxicity than every eight hours administration (26).

3.3. Therapeutic Drug Monitoring (TDM)

For each drug with a low therapeutic index and a poor correlation between dose and concentration, TDM may help clinician in achieving target concentrations. It seems rational to use TDM for AGs, especially when administered in patients with day-to day variation in their metabolic capacity like preterm neonates and infants to improve the dosing of AGs. On the other hand, if a dosing regimen is associated with predictable concentrations, the TDM may not be necessary anymore. The role of therapeutic drug monitoring (TDM) in EID of AGs is not clear. In spite of evidences supporting the use of TDM in neonates (27, 28) and adults (29, 30), there are several studies that propose routine TDM is not necessary in practice. In a cohort of 79 children (median age: 5.6 years), gentamycin 7 mg/kg/day was administered as EID. Most children received gentamycin for febrile neutropenia. Permanent hearing loss occurred in two patients (1.88%) and only one patient (0.94%) experienced transient nephrotoxicity. Serum gentamycin levels were in the normal limit, even in those experienced toxicity. Interestingly, TDM using a nomogram was not effective in predicting or preventing toxicity (31). It has been demonstrated that routine early therapeutic drug monitoring does not improve tobramycin dosing in neonates when the dose was based on their gestational age as follows; 3.5 mg/kg every 24 hours for neonates less than 28 weeks, 2.5 mg/kg every 18 hours for neonates between 28 - 36 weeks and 2.5 mg/kg every 12 hours for neonates older than 36 weeks (32).

Similar result of less use of TDM in reducing nephrotoxicity of AGs was shown in adult patients with severe sepsis. Other factors including hemodynamic instability, inter and intra variation of drug pharmacokinetic/pharmacodynamic characteristics, increased volume of distribution and increased or decreased elimination constant should be considered in critically ill patients who receive AGs and the shock per se may deteriorate the kidney function, independent of AG trough level (12). In fact, other confounding etiologies of renal impairment may decrease the importance of TDM in critically ill patients.

4. Conclusions

EID of AGs is an appropriate dosing method for achieving a desired peak and trough concentrations in neonates. Considering its safety profile, the need for TDM may be reduced with EID in infants who receive AGs for less than 72 hours. TDM should be considered for patients who need to receive AGs more than 72 hours. The risk of serum drug concentration outside the therapeutic range is lower in neonates and pediatrics treated with EID.

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