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REVIEW ARTICLE

Once Daily Dosing of Aminoglycosides in Pediatric Cystic Fibrosis Patients: A Review of the Literature

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Patients with cystic fibrosis receive many courses of antibiotic therapy throughout their lifetime. Dosing aminoglycosides once daily has become common practice in many of these individuals. Due to ease of home administration, decreased nursing time, and improved quality of life, this regimen is being increasingly explored in the cystic fibrosis population. Because patients with cystic fibrosis have increased aminoglycoside clearance, once daily dosing may result in a prolonged time during the dosing interval when concentrations of the drug may be undetectable. This makes the use of once daily dosing of these antibiotics in patients with cystic fibrosis controversial. Although aminoglycosides exhibit a post antibiotic effect, the duration of this effect is unknown in humans; therefore, the development of resistance to the aminoglycoside is a concern. This manuscript will review the organisms most commonly associated with a pulmonary exacerbation of cystic fibrosis, the properties of the aminoglycoside that make once daily dosing feasible, the concept of once daily dosing in those with cystic fibrosis and the current literature regarding efficacy, monitoring, toxicity and concerns of resistance with once daily dosing in this population.

KEYWORDS aminoglycosides, cystic fibrosis, once daily

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INTRODUCTION

Patients with cystic fibrosis (CF) receive repeated, extended courses of aminoglycoside antibiotic therapy over their lifetime. This makes them susceptible to the cumulative adverse effects of nephrotoxicity and ototoxicity. Traditionally, these medications are given every eight hours. However, once daily (OD) administration would simplify home administration of antibiotics and decrease nursing time, providing cost savings and overall increased quality of life. Studies have shown that OD aminoglycoside dosing has a lower incidence of adverse effects with equivalent efficacy in non-CF populations.[1] Due to the increased volume of distribution and shorter half-life of aminoglycosides in the CF population, it is highly debated if this is a sufficient regimen for these patients, given that concentrations would be below the minimum inhibitory concentration (MIC) for more than half of the dosing interval. This paper will review the literature regarding the safety, efficacy and monitoring of OD dosing of aminoglycosides in the pediatric CF population.

ABBREVIATIONS CF, cystic fibrosis; FEF25%-75% , forced expiratory flow in mid expiration; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MIC, minimum inhibitory concentration; NAG, N-acetyl-D glucosaminidase; OD, once daily; PAE, post antibiotic effect; PFT, pulmonary function tests; TID, three times daily

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BACTERIAL ORGANISMS IN CYSTIC FIBROSIS

Cystic fibrosis patients will become colonized and infected with many bacteria over the span of their lives, requiring numerous courses of antibiotic therapy. The most common organisms colonizing younger children include *Haemophilus influenzae* and *Staphylococcus aureus*.[2] *Pseudomonas aeruginosa*, an opportunistic Gram-negative organism, will colonize most patients with CF by the time they are six years of age.[2] Once colonized with *P aeruginosa*, a CF patient generally has a decline in pulmonary function, often leading to increasing frequency of pulmonary exacerbations requiring multiple courses of antibiotics. *P aeruginosa* has multiple regulatory pathways and virulence factors that allow it to adapt and thrive in the lungs of CF patients.[3] One of these is the ability to form biofilms, which are a growth mode of bacteria resulting in clusters of microcolonies encased in a biopolymer matrix that attach to a surface.[4] Biofilm formation is what allows many strains of *P aeruginosa* to thrive in the CF lung and resist treatment by antibiotics.[5] Following prolonged colonization with *P aeruginosa*, the host inflammatory response causes increases in alginate synthesis, converting non-mucoid strains to alginate-producing mucoid strains.[6] The alginate anchors the *P aeruginosa* to the respiratory epithelium.[6] Although its role in antibiotic resistance is controversial, it has been theorized that the alginate forms an exopolysaccharide barrier which interferes with antibiotic penetration, protects *P aeruginosa* from phagocytosis, and attenuates the host reponse.[5-7] To overcome these factors of bacterial resistance, CF patients are often treated with high dose combination antibiotic therapy. This combination therapy, often including an aminoglycoside, has been shown to provide a synergistic effect in vitro and may limit the emergence of antibiotic resistant strains of *P aeruginosa*.[8,9]

Atypical organisms including *Stenotrophomonas maltophilia* and *Burkholderia cepacia* can also colonize the lungs of CF patients. These organisms are often highly resistant to standard CF antibiotic regimens and must be treated aggressively with multiple antibiotic combinations. Patients colonized with *B cepacia* will often have synergy testing performed to guide antibiotic treatment. Although aminoglycosides are often part of the treatment regimen for these atypical organisms, current studies of OD aminoglycosides have excluded patients colonized with *B cepacia*.

AMINOGLYCOSIDES

Properties

Aminoglycosides inhibit bacterial protein synthesis by binding the 30s and 50s ribosomal subunits resulting in a defective bacterial cell membrane.[10] They provide bactericidal aerobic Gram-negative coverage and are often used in combination with another antibiotic, usually a beta-lactam. The use of two agents provides synergy and slows the emergence of resistance.[11]

Aminoglycosides exhibit concentration-dependent killing; therefore, increased peaks equal increased efficacy.[12] They are commonly administered in the United States as intermittent 30- to 60-minute infusions.[10] Aminoglycosides are widely distributed into most body fluids including synovial, peritoneal, ascitic, and pleural fluids.[10] They are primarily eliminated unchanged by the kidney.[10] Pediatric patients exhibit increased clearance and volume of distribution when compared to adults.[10]

Toxicity

Ototoxicity due to an aminoglycoside is associated with elevated peak serum concentrations. Ototoxicity generally occurs only with large doses or when renal insufficiency is present. Ototoxicity manifests itself as auditory and vestibular symptoms and is often irreversible.[10] Several risk factors are associated with a higher incidence of ototoxicity. These include duration of treatment, cumulative dose, average daily dose, elevated peak serum concentrations, concurrent use of diuretics, underlying diseases and previous exposure to an aminoglycoside.

Nephrotoxicity due to aminoglycoside therapy presents itself most often as non-oliguric renal failure.[10] Common findings are decreased glomerular filtration rate, increased serum creatinine, increased blood urea nitrogen and impaired ability to concentrate urine. In most patients, nephrotoxicity is reversible. Patients

with CF are commonly prescribed regimens of long duration with large doses and repeated exposure throughout their lives, increasing the risk of ototoxicity and nephrotoxicity.

Characteristics of OD dosing

There are many characteristics of aminoglycosides that favor OD dosing. Elevated serum concentrations should allow for concentration-dependent killing.[13] Aminoglycosides exhibit post antibiotic effect (PAE) which is the continued suppression of bacterial growth even after the drug concentration is below the MIC of the organism.[13,14] The duration of this phenomenon is unknown but a period of up to ten hours has been documented in animal studies.[15] Post antibiotic effect increases with increased serum concentrations; therefore, OD dosing could theoretically provide a longer PAE.[16] Adaptive resistance is also seen with aminoglycosides, meaning that Gram-negative organisms exhibit decreased drug uptake after initial exposure.[17,18] This reduction of uptake decreases bacterial killing. Adaptive resistance is thought to be reversible after an extended duration of low drug concentration. Studies suggest that in other patient populations OD dosing reduces adaptive resistance.[19]

It has been proposed that OD aminoglycoside dosing could potentially decrease aminoglycoside-associated nephrotoxicity and ototoxicity. Nephrotoxicity occurs primarily in the proximal tubule.[10] Elevated serum concentrations saturate the uptake of aminoglycosides in the proximal tubule.[13] Therefore, OD dosing should theoretically decrease nephrotoxicity by decreasing the overall uptake of the antibiotic. Once daily dosing of these agents also produces increased concentrations in the ear; however, the increased interval allows adequate time for drug clearance and a decreased likelihood of drug accumulation. Although patients with CF are generally at greater risk for ototoxicity due to the need for higher peak serum concentrations, OD dosing could potentially decrease the incidence of ototoxicity in these patients.

Use in CF

Aminoglycosides are most commonly used in CF patients in combination with a beta- lactam to treat *P aeruginosa*.[20] Patients with CF have an even greater increase in clearance and volume of distribution than non-CF pediatric patients.[21] These pharmacokinetic differences require that CF patients receive larger doses than other patient populations. Penetration into the lung tissue is essential in treating CF patients; therefore, higher peak serum concentrations are needed for lung penetration. For example, a typical non-CF pediatric patient will receive tobramycin 2.5 mg/kg/dose every 8 hours, producing peak serum concentrations of 5 to 8 mg/L, whereas a CF patient will receive around 3.3 to 4 mg/kg/dose every 8 hours producing peaks of 8 to 12 mg/L.

STUDIES IN THE LITERATURE

Efficacy

The desired outcome of intravenous antibiotic therapy in pulmonary exacerbations of CF is improvement in a number of parameters including pulmonary function tests, respiratory symptoms, and nutritional markers. As stated earlier, OD dosing of aminoglycosides have been studied in pediatric CF patients with no change seen in efficacy or toxicity. The studies discussed in the following section of the manuscript are summarized in the Table.

In 1998, Vic and associates randomized 22 CF patients to receive 15 mg/kg/day of tobramycin, divided into 3 doses or given as OD. All patients also received ceftazidime 200 mg/kg/day for 14 days.[22] All patients met criteria for a pulmonary exacerbation and none had documented colonization of *B cepacia* or *S maltophilia*. The patients had chronic colonization with *P aeruginosa*, defined by at least 3 positive sputum cultures over the previous 6 months. Subjects ranged from 5 to 19 years. Serum tobramycin concentrations were measured and compared to sputum levels. No dosage adjustments were made during the course of the study. Sputum concentrations were significantly higher in the OD group. Outcomes were assessed on day 1 and day 14. Although statistically significant improvement was noted in forced vital capacity (FVC), forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$), weight/height ratio, and plasma prealbumin for both groups, no difference was noted between groups, thus the authors concluded that the OD regimen was equally efficacious to three times daily dosing.[22]

Table. Comparative Efficacy of Once Daily versus Three Times Daily Tobramycin

Reference	Change in FEV_1 (%)		P value	Change in FVC (%)		P value	Change in FEF_{25-75} (%)		P value
	OD	TID		OD	TID		OD	TID	
Vic[22]	14.9 ± 16	14 ± 15.3	NS	13.8 ± 15	10.5 ± 13	NS	12.9 ± 14.8	21 ± 22	NS
Smyth[23]	21.9 ± 30.5	22.1 ± 30.1	NS	NR	NR	NR	NR	NR	NR
Master[30]	10.6 ± 8.5	12.8 ± 13.5	NS	9.9 ± 9.1	12.1 ± 12	NS	10.6 ± 9.6	13.7 ± 16.5	NS

FEF_{25-75}%, Forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1, Forced expiratory volume in one second; FVC, Forced vital capacity; NR, Not Reported; NS, Not significant; OD, once daily; TID, three times daily

A randomized double blinded study compared a OD strategy to a traditional three times per day regimen.[23] The patients received tobramycin plus ceftazidime for 14 days. Patients older than 5 years of age who were diagnosed with a pulmonary exacerbation with documented *P aeruginosa* in sputum cultures susceptible to tobramycin or ceftazidime were eligible for inclusion. Patients with pre-existing renal or hearing impairment, previous infection with *B cepacia*, or hypersensitivity to tobramycin or ceftazidime were excluded from study. Efficacy was measured as change in forced expiratory volume in 1 second (FEV_1) determined as a percentage of the predicted FEV_1 based on individual demographics. Other factors included: improvement over baseline FEV_1, C-reactive protein concentration, a clinical score based on symptoms and physical findings, and time to next antibiotic course. Enrollment of 219 patients yielded a sample size large enough to prove equivalency (with a 95% confidence interval) of therapy based on a 4% or smaller difference between groups of predicted FEV_1. Dosing was based on total daily tobramycin requirements from previous pharmacokinetic assessments for each patient, although actual dose in these patients was not discussed. Patients who were naïve to aminoglycoside therapy were initiated on 10 mg/kg/day. Patients with trough serum concentrations that were higher than the target range were withdrawn from the study. Patients with peak serum concentrations outside of the target range were adjusted by a 10% increase or decrease accordingly. Actual pharmacokinetic adjustments or withdrawal of patients whose peak and trough concentrations were outside of the goal range were not reported. With a difference between groups of 0.4%, there was statistical equivalency between regimens in mean improvement of predicted FEV_1 from days 1 to 14. There was no difference in any of the other efficacy measures. This analysis remained true when groups where stratified into pediatric and adult subgroups.[23]

In 2006, a Cochrane review was published examining the efficacy of OD dosing of tobramycin compared to three times daily dosing of tobramycin.[24] For inclusion in the review, studies were required to evaluate CF patients experiencing a pulmonary exacerbation as defined by Fuchs and colleagues.[25] Primary outcomes were pulmonary function tests (PFTs), including FEV_1, FVC, and $FEF_{25\%-75\%}$. Numerous secondary outcomes were also recorded. The group identified 11 studies that met search characteristics, of which 4 met inclusion criteria for the review. Two of the four have already been included in this review. The remaining studies included a three arm, open-label, crossover study performed by Riethmuller et al., which was published in abstract form only.[26] A second investigation was an open label parallel study of adult CF patients by Whitehead and colleagues.[20] The Cochrane review concluded that there is no difference in efficacy between OD and three times daily tobramycin when given with a beta-lactam agent in CF patients with a pulmonary exacerbation.[24]

Monitoring

Monitoring guidelines for OD aminoglycoside administration were included in the United Kingdom CF Trust Addendum for Antibiotic Treatment for Cystic Fibrosis.[27] These guidelines stated that a peak serum concentration should only be obtained for patients with *P aeruginosa* that demonstrates intermediate sensitivity to tobramycin.[27] They also recommended that renal function testing should be performed before the first dose of tobramycin and repeated before the eighth dose. In order to ensure adequate clearance of the aminogly-

coside, a trough serum concentration should be obtained before the second and eighth doses.[27] Goals for tobramycin concentrations are 20-30 mg/L and less than 1 mg/L for peaks and troughs, respectively. One concern with these recommendations is the lack of information of regarding the total time the patient may have an undetectable serum concentration (i.e., below the MIC and outside of the PAE).

Massie and Cranswick published a pharmacokinetic profiling of OD tobramycin in which they administered 12 mg/kg/dose OD, in addition to ticarcillin/clavulanic acid, to 44 pediatric patients during the course of 86 admissions.[28] The authors determined a volume of distribution of 0.267 L/kg, clearance of 0.103 L/kg/hr, and half-life of 1.82 hours.[28] Based on this study, a nomogram was developed recommending that a single serum concentration be determined 1 to 6 hours after administration.[28] Nomograms allow for accurate prediction of peak and trough serum concentration values ensuring efficacy and monitoring for potential toxicity. In other patient populations, nomograms have allowed for accurate and easy dose adjustment of an aminoglycoside based on a single serum concentration. In the future, if OD dosing becomes a standard of practice in those with CF, a validated nomogram would assist practitioners.

There are no widely accepted evidence based guidelines regarding monitoring of OD aminoglycosides in pediatric patients, especially those with CF. Once daily dosing in the pediatric CF population is new to many institutions and the existing monitoring protocols vary greatly. Hopefully, as more CF centers adopt this practice, evidence based guidelines for monitoring can be developed based on knowledge gleaned from using this regimen in pediatric CF patients.

Resistance

As previously discussed, appropriate OD dosing of an aminoglycoside will result in peak serum concentrations greater than 10 times the MIC, as well as undetectable trough concentrations each day. This regimen has demonstrated a reduction in adaptive resistance,[19] which is believed to be the result of temporary bacterial down-regulation of aminoglycoside uptake. With the prolonged dosing interval and extended drug-free interval, this down-regulation is theoretically reduced. Due to the advantageous property of PAE exhibited by this class of drugs, bacteriostatic activity continues long after the aminoglycoside is no longer measurable in serum. However, even with peak tobramycin serum concentrations of 40 mg/L, the concentration of the drug may be undetectable for up to 12 hours in some patients. This exceeds the duration of the known PAE. Resistance in CF patients is also related to the development of biofilms by *P aeruginosa*. The creation of these biofilms is thought to occur during chronic colonization and exposure to drug concentrations below the MIC.

To date, only one study has published changes in MIC when comparing OD to traditional aminoglycoside dosing in CF patients.[29] This study involved 33 adults and confirmed the results of previous studies in regards to equal efficacy between the two dosing methods. These investigators also demonstrated a statistically significant increase (an average of 6.8 mg/L) in MIC from day 1 until day 14 of therapy in the OD group compared to no change in the conventional three times daily group. The authors theorize that this increase in resistance is linked to the extended dosing interval. Since eradication of *P aeruginosa* in chronically colonized CF patients is unlikely, patients who develop multidrug-resistant strains have a worse prognosis than those who do not. This change in resistance deserves larger and more direct study in CF patients to ensure long term efficacy of antibiotic treatment and prevent therapeutic failure secondary to the emergence of multi-drug resistant organisms.[29]

Toxicity

Nephrotoxicity

Two randomized trials monitored nephrotoxicity using changes in serum creatinine from baseline, and excretion of N-acetyl–D glucosaminidase (NAG), an enzyme excreted by the proximal tubule.[23,30] One of the studies found no change in creatinine concentration over the treatment course, but did find a significant increase in NAG excretion among the three times daily treatment group.[30] In the other study, creatinine concentrations decreased in the OD group; this finding was significant among the pediatric patients.[23]

This study also found a significantly smaller increase in NAG among the once daily group.[23] Vic et al. measured proteinuria, lysozymuria, β_2 microglobulinuria, and creatinine clearance.[22] Proteinuria and creatinine clearance did not change. Lysozymuria increased in both groups but remained within the normal limits. Microglobulinuria increased in both groups; however, the three times daily group exhibited a greater increase, although still within normal limits ($P < .01$).[22] Whitehead et al. monitored renal toxicity using serum creatinine, magnesium and potassium concentrations.[20] No significant change was noted between the groups. Overall, no clinically significant difference in nephrotoxicity was observed between the two regimens.

Ototoxicity

With regard to ototoxicity, audiometry at low and high frequency was performed in most studies and patients were asked to subjectively report symptoms of vestibular ototoxicity. One study did report transient vestibular ototoxicity in one patient; however, this patient received 15 mg/kg over 5 minutes resulting in a fifteen minute post-dose serum concentration of 61.2 mg/L.[31] The symptoms resolved after the concentration decreased. Infusing any aminoglycoside over 5 minutes is not a typical practice in the United States. Another randomized trial found tinnitus in two patients from each group (OD and three times daily).[30] All 4 cases were attributed to a rapid administration rate and did not recur upon administration at a slower rate. In another study, 2 patients, one from the control and one from the OD group, experienced acute dizziness causing withdrawal from the study.[23] In both of these patients, the symptoms resolved. These researchers published an additional evaluation of ototoxicity in this same patient population. They concluded more sensitive pre- and post-treatment pure tone audiometry testing were needed.[32] Their goal was to detect any subtle changes over the 14-day course of tobramycin. They also performed a 6- to 8-week follow up in a subset of patients. No difference was seen between baseline and post-treatment, nor was there a difference seen between the OD and three times daily group.[32] Another study of audiograms at baseline and two weeks post-treatment found one patient in each group (OD and conventional) with hearing impairment after treatment.[20] Overall, although some ototoxicity was found in the studies, it was most often transient and not deemed clinically significant. Further long term studies are needed to assess the risk of cochleotoxicity upon repeated exposure to OD dosing of aminoglycosides.

CONCLUSIONS

Review of the published literature evaluating OD aminoglycoside dosing for pediatric CF patients reveals relatively small, short term studies with little evaluation of long term effects on the management of the disease. These studies universally conclude that there is no difference in efficacy between OD and three times daily dosing. Measures of pulmonary function improve over the same amount of time and to the same degree regardless of dosing strategy. Great strides in treatment that have occurred over the last several decades have prolonged the life expectancy of CF patients to greater than 30 years. Further follow-up over longer periods of time will be required to determine if OD aminoglycoside dosing will have any significant impact on overall prognosis, especially in light of reports of increased resistance following OD therapy.[29] Although not demonstrated in a large study, early development of multi-drug resistant *P aeruginosa* in patients receiving OD regimens for exacerbations would certainly be detrimental to this patient population and could be a deterrent to widespread adoption of this practice. In terms of toxicity, studies agree that OD administration does not demonstrate an inferior/worse safety profile than conventional dosing. In fact, some studies demonstrate reduced nephrotoxicity demonstrated by laboratory evaluation. This is consistent with observations using OD dosing in other patient populations. Although ototoxicity is more difficult to evaluate, there does not appear to be a difference between the two dosing methods.

There is no consensus on therapeutic drug monitoring in patients receiving OD therapy. The publication of a nomogram designed from pharmacokinetic evaluation of these patients has not led to agreement on timing or frequency of serum concentrations, nor on dosing adjustments based on unexpected serum concentra-

tions. Many centers are obtaining mid-interval concentrations just to ensure that the aminoglycoside concentrations are not undetectable after 12 hours. Until a true assessment of the duration of the PAE of aminoglycosides in humans is done, it will be difficult to create pharmacokinetic goals in these patients.

Finally, a need exists for a large multicenter evaluation of OD aminoglycoside therapy in CF that includes several years of follow-up. Increased resistance, long term lung function, and cumulative toxicity all deserve special attention. All studies to date have excluded patients with *B cepacia*, which is excluding the very patients with the most frequent and serious exacerbations. Aminoglycosides are used often in the treatment of *B cepacia*, therefore, these patients should be included in future studies. Although the OD regimen would simplify and improve quality of life for this patient population, care must be taken to ensure that these patients are not being placed at risk for multi-drug resistant organisms and cumulative toxicities.

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