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Does Circadian Rhythm Affect the Pharmacokinetics of Once-Daily Tobramycin in Adults With Cystic Fibrosis?

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Background: In the era of multiple daily dosing of systemic aminoglycosides, a circadian rhythm in the clearance of these vital antibiotics has been demonstrated in animals and healthy volunteers. Over the past decade, once-daily dosing regimens have been proved to be less nephrotoxic and were therefore adopted worldwide for most indications requiring treatment with an aminoglycoside. In this study, the effect of the time of administration on the pharmacokinetics of once-daily tobramycin in adults with cystic fibrosis (CF) experiencing a pulmonary exacerbation was investigated.

Methods: In this open randomized study, patients with CF received intravenous tobramycin at 8:00 or 22:00 hours. Pharmacokinetic and kidney function parameters were compared between the 2 groups.

Results: Twenty-five patients were included. The mean weight-corrected clearances of tobramycin were 1.46 versus 1.43 mL/h*kg ($P = 0.50$) and mean volumes of distribution were 0.25 versus 0.27 L/kg ($P = 0.54$) for the 8:00 and 22:00 groups, respectively. In addition, no significant differences were detected in changes in estimated clearances of creatinine or tobramycin on day 1 and day 8 in the 8:00 or 22:00 group, indicating that there was no decline in clearance over time. At day 8 of therapy, the increase in serum blood urea nitrogen in the 22:00 group was significantly higher than that in the 8:00 group (1.8 versus 0.2 mmol/L, $P = 0.015$).

Conclusions: The time of administration (8:00 versus 22:00) did not affect tobramycin pharmacokinetics in the adult CF population studied. The increase in serum blood urea nitrogen in the 22:00 group requires further investigation.

Key Words: tobramycin, circadian rhythm, cystic fibrosis

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The authors declare no conflict of interest.

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BACKGROUND

Cystic fibrosis (CF) is an incurable, genetically inherited disease that causes changes in ion transport mechanisms in various parts of the body, including the lungs and skin. Although the disease affects several body systems, it is respiratory decline that leads to fatality.¹ Patients with CF are prone to acquire pulmonary infections with *Pseudomonas aeruginosa* and other microorganisms; these infections are associated with irreversible pulmonary damage, leading to reduced life expectancy.² Intravenous aminoglycosides in combination with beta-lactam antibiotics are a cornerstone for the treatment of exacerbation of chronic pulmonary infections caused by *P. aeruginosa*.³ However, frequent use of intravenous aminoglycosides is associated with nephrotoxicity, ototoxicity, and vestibulotoxicity in some cases.^{4,5} Repeated or prolonged dosing may cause damage to the proximal tubuli, resulting in renal impairment, which affects up to 42% of adults with CF.⁶ Owing to the extension of life expectancy in patients with CF through improved treatment, aminoglycoside-induced cumulative toxicity is more relevant nowadays than that in the past. The TOPIC study demonstrated that once-daily dosing (ODD) of tobramycin is as effective as and may be less toxic than multiple daily dosing in patients with CF.⁷ Hence, ODD of tobramycin has been adopted by many CF centers worldwide. Because aminoglycosides are almost completely excreted into the urine by glomerular filtration, their kinetics may fluctuate with diurnal changes in kidney function as previously demonstrated in animal experiments^{8,9} and healthy volunteers.^{8,10} If a similar effect exists in patients with CF, it will be clinically more relevant in ODD than in multiple daily dosing regimens. Nevertheless, human data on the circadian rhythm in pharmacokinetics of drugs are conflicting and whether an association is present primarily seems to depend on the dosing regimen and specific population investigated.^{11–13} In a recent study in children with CF, the time of administration (morning versus evening) showed no effect on drug clearance, but higher urinary kidney injury molecule-1 (KIM-1) levels were detected in the evening dosage group than in the morning group.¹⁴ To date, the effect of diurnal changes on aminoglycoside pharmacokinetics in adults with CF has not been studied prospectively. It is important that patients with CF are exposed to aminoglycosides at the period of highest clearance to prevent acute adverse events and events resulting from accumulated toxicity, without compromising efficacy.^{15,16} In the present randomized clinical study, we aimed to evaluate the presumed

diurnal changes in tobramycin pharmacokinetics and kidney function associated with the time of administration.

METHODS

Study Design and Protocol

Patients with CF treated with intravenous tobramycin for a pulmonary exacerbation were included in this open randomized clinical trial (Dutch Trial Register number: NTR3309). The study was approved by the local medical ethics committee. The study was powered to detect a 25% difference in tobramycin exposure quantified by the area under the concentration–time curve (AUC) because regulatory authorities consider 80%–125% limit to be a clinically relevant cutoff for bioequivalence testing. Informed consent was obtained from all participants. The inclusion criteria were age greater than 18 years, a diagnosis of CF, chronic infection with *P. aeruginosa*, with the most recently isolated organism showing sensitivity to tobramycin, and pulmonary exacerbation as previously defined.¹⁷ The exclusion criteria were administration of other nephrotoxic drugs, allergy to aminoglycosides, pregnancy, granulocytopenia ($<1.0 \times 10^9/L$), estimated glomerular filtration rate (eGFR) < 40 mL/min, or pre-existing hearing impairment. After inclusion, the participants were randomly assigned to receive tobramycin at either 8:00 or 22:00 hours. Tobramycin (10 mg/kg) was administered daily as a 30-minute infusion. Blood samples were drawn 1 hour after the start of infusion (peak) and between 6–8 hours after the start of infusion. The dosage regimens were altered if serum concentrations were outside the target values (peak: 25–30 mg/L; extrapolated trough <0.5 mg/L). Tobramycin pharmacokinetic parameters at days 1 and 8 were calculated for each patient using a previously described 1-compartment model with linear pharmacokinetics designed specifically for adolescent and adult patients with CF¹⁸ and MW/Pharm pharmacokinetic software package version 3.60.¹⁹ Volume of distribution (Vd), tobramycin clearance (CL_{Tob}), and AUC were compared between the groups. Furthermore, the change in CL_{Tob} from day 1 to day 8 was compared between the 8:00 and 22:00 hour groups. Serum creatinine concentrations and blood urea nitrogen (BUN) were determined in the morning on days 1 and 8 of tobramycin treatment. Subsequently, kidney function was quantified at baseline and at day 8 using serum creatinine concentrations to estimate creatinine clearance using the formula proposed by Jelliffe,²⁰ which approximates the eGFR. The effect of the time of administration of tobramycin on kidney function was assessed by the comparison of change in serum BUN and eGFR between the 8:00 and 22:00 groups.

Statistical Analyses

A Kolmogorov–Smirnov test was used to identify the normal distribution of data. Mean values and SDs of continuous variables are presented in normal distributions; otherwise, medians and ranges were reported. A Student *t* test was used to determine statistical differences among normally distributed data. If data were not normally distributed, a Mann–Whitney *U* test was performed. A χ^2 test was used to

compare dichotomous variables between the groups. Vd and CL_{Tob} were analyzed after correction for body weight; AUCs were normalized to an administered dose of 500-mg tobramycin. The tests were 2-tailed, and a *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA, USA).

RESULTS

Patient Characteristics

Twenty-five patients who received at least 1 dose of tobramycin were enrolled in the study. No significant differences in baseline characteristics were detected between the 8:00 and 22:00 groups (Table 1). Treatment was either stopped or continued at home after discharge for 2 patients during the first week of tobramycin therapy in either study arm. Tobramycin dose was adjusted at day 1 in 3 and 5 patients in the 8:00 and 22:00 groups, respectively. The median cumulative doses over 7 days of tobramycin therapy were 3980 and 3840 mg (*P* = 0.90) for the 8:00 and 22:00 groups, respectively. The patients did not receive other nephrotoxic medications from day 1 to day 8.

Pharmacokinetics

Based on the concentrations drawn, no significant differences in pharmacokinetic parameters were detected between the 8:00 and 22:00 groups (Table 2 and Fig. 1). No significant difference was observed in change in CL_{Tob} between day 1 and day 8 in the 8:00 (*P* = 0.58) or 22:00 (*P* = 0.67) group, indicating that there was no decline in clearance over time (Fig. 2).

Parameters of Kidney Function

No significant differences in change in the eGFR from baseline were found between the 8:00 and 22:00 groups (3.8 versus 10.0 mL/h respectively, *P* = 0.85). The 22:00 group showed a significant increase in serum BUN compared with

TABLE 1. Baseline Characteristics of the 8:00 and 22:00 Groups

	Time of Administration		<i>P</i>
	8:00	22:00	
No. of patients	12	13	
Age (yr)	30 (12)	30 (11)	0.42*
Male sex (%)	63.6	72.7	0.87‡
Weight (kg)	60 (21)	61 (22)	1.0*
Serum creatinine (nmol/mL)	66 (55–97)	65 (33–91)	0.46†
eGFR (mL/min)	118 (67–132)	112 (82–175)	0.60†
cGFR (mL/min)	102 (75–145)	108 (55–185)	1.0†
BUN (nmol/mL)	4.2 (2.2–7.7)	4.0 (2.3–6.3)	0.27†

cGFR, glomerular filtration rate calculated using a 24 hour urine collection.

Dichotomous variables were expressed as percentages and continuous variables were expressed as means or medians, with SDs or ranges given in parentheses.

*Student *t* test.

†Mann–Whitney *U* test.

‡Chi-square test.

TABLE 2. Dosing and Pharmacokinetic Parameters Are Presented as Means or Medians With SDs or Ranges Given in Parentheses, Respectively

	Time of Administration		<i>P</i>
	8:00	22:00	
Day 1			
Dose	525 (420–600)	500 (400–600)	0.35†
Cl _{TOB} (mL/min/kg)	1.46 (0.44)	1.43 (0.52)	0.50*
Vd (L/kg)	0.25 (0.08)	0.27 (0.09)	0.54*
AUC (mg*h/L)‡	87 (67–134)	97 (70–137)	0.21†
Day 7			
Dose	500 (500–720)	550 (400–640)	0.39†
Cl _{TOB} (mL/min/kg)	1.42 (0.52)	1.54 (0.63)	0.87*
Vd (L/kg)	0.25 (0.09)	0.27 (0.11)	0.19*
AUC (mg*h/L)‡	101 (70–136)	88 (70–138)	0.34†

Cl_{TOB}, clearance of tobramycin; V_d, volume of distribution.

*Student *t* test.

†Mann–Whitney *U* test.

‡Normalized to a tobramycin dose of 500 mg.

the 8:00 group (1.8 versus 0.2 mmol/L, *P* = 0.015). Serum BUN at day 8 was significantly higher than the baseline in the 22:00 group (*P* = 0.014), but not in the 8:00 group (*P* = 0.79).

DISCUSSION

In this study, we aimed to determine the effect of the time of administration on the pharmacokinetics of once-daily tobramycin in adults with CF experiencing a pulmonary exacerbation. Our results showed that the time of administration (8:00 versus 22:00) had no influence on tobramycin pharmacokinetics. However, the 22:00 group showed a significant increase in serum BUN after 1 week of therapy when compared with the 8:00 group; further investigation is required to determine the possible reasons for this.

This is the first study to examine the effect of diurnal changes on the pharmacokinetics of tobramycin in adults with CF. The pharmacokinetic results in our study were unexpected because 3 of 5 previous studies in hospitalized patients reported that the circadian rhythm has an influence on renal clearance of aminoglycosides.^{11–13} However, these 3 positive studies were performed in an era where aminoglycosides were multiple daily or even continuously dosed. In addition, these studies investigated amikacin, kanamycin, and gentamicin, which are more likely to accumulate than tobramycin.^{7,21} Moreover, in most of the studies mentioned previously, peak and trough concentrations were used for the estimation of pharmacokinetic parameters.^{7,12,21} With an actual aminoglycoside trough concentration of 0.5 mg/mL, most assays report a value somewhere between 0 and 1.0 mg/mL. The use of an inaccurate value may have major consequences in the calculation of clearance. For optimal estimation of tobramycin pharmacokinetics, a peak level and a second level at 1.44 half-lives after the end of administration should be drawn (ie, between 1.5–9 hours for an adult with CF).²²

As this study was performed in a hospitalized population, patients who have a less pronounced circadian rhythm

FIGURE 1. The graphs are box-and-whisker plots of tobramycin clearance (Cl_{TOB}, A), volume of distribution (V_d, B), and AUC (C). The line in the middle of each box represents the median; the box extends from the 25th to 75th percentile (interquartile range); and whiskers extend to 1.5 times the interquartile range, rolled back to where data are present.

FIGURE 2. The graph is a box-and-whisker plot of eGFR and serum BUN. The line in the middle of each box represents the median; the box extends from the 25th to 75th percentile (interquartile range); and whiskers extend to 1.5 times the interquartile range, rolled back to where data are present.

owing to an altered status of the immune system may also have been selected.²³ Perhaps, the circadian rhythm in the ambulatory-treated CF population is preserved during a pulmonary exacerbation. Vinks et al²⁴ found that early morning serum concentrations of ceftazidime were significantly higher than the afternoon concentrations in patients with CF who were treated at home with a continuous infusion. Nevertheless, most patients with CF worldwide will get admitted in case of a pulmonary exacerbation, requiring treatment with intravenous antibiotics. Finally, the contribution of the effect of the circadian rhythm may be limited because of the rapid renal clearance of tobramycin in patients with CF compared to patients with non-CF.¹⁸

The main limitation of this study is that a 1-compartment model with linear pharmacokinetics was used; the use of a multicompartment pharmacokinetic model would be advised in future studies. In addition, the samples were not available to include high information data in the terminal phase. Nevertheless, the terminal phase includes only a minor part of tobramycin exposure.¹⁸

Despite the lack of an observed effect of administration time on the pharmacokinetics of tobramycin, we found a significant rise in serum BUN in the 22:00 group compared with the 8:00 group. A rise in serum BUN of 1.8 nmol/mL may not be considered clinically relevant and is in line with the urinary KIM-1 increase detected in children with CF. However, it is rather unexpected because the eGFR and exposure in terms of AUC were the same for the 8:00 and 22:00 groups. The former is possibly caused by a disturbance in the diurnal pattern of serum BUN and/or KIM-1 due to nightly exposure to tobramycin, resulting in an increase in these biomarkers to peak values in the morning when sampling takes place.²⁵ Polycationic aminoglycosides such as tobramycin can alter glomerular ultrastructure, permeability, and reabsorption.²⁵ Finally, a “false” rise in serum BUN or any other biomarkers caused by interference of tobramycin

with the analytical assay of BUN should not be overlooked. As a result of the known circadian rhythm of biochemical parameters, sampling of these parameters should be performed at several time points during the day or as a 24-hour urine collection. Future studies addressing this issue should preferably investigate longer periods of tobramycin exposure and focus on sampling of highly sensitive as well as thoroughly characterized biomarkers for renal toxicity, such as cystatin C, β -2-microglobulin, and N-acetyl- β -D-glucosaminidase, throughout the day.^{26,27} In the present study, the time of administration had no effect on tobramycin pharmacokinetics in the hospitalized adult CF population. A previous study in healthy volunteers showed no difference in creatinine levels, which further supports the outcome of our study.²⁸ An unexpected significant rise in serum BUN after 1 week of therapy was detected in the group that received tobramycin during the resting period compared with the active period; this should be investigated further.

CONCLUSIONS

The time of administration (8:00 versus 22:00) did not affect tobramycin pharmacokinetics in the adult CF population studied.

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REFERENCES

1. Tiddens HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol.* 2002;34:228–231.
2. Emerson J, Rosenfeld M, McNamara S, et al. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol.* 2002;34:91–100.
3. Tan KHV, Hyman-Taylor P, Mulheran M, et al. Lack of concordance in the use and monitoring of intravenous aminoglycosides in UK cystic fibrosis centres. *Pediatr Pulmonol.* 2002;32:165.
4. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother.* 1996;37:4.
5. Scheenstra RJ, Rijntjes E, Tavy DL, et al. Vestibulotoxicity as a consequence of systemically administered tobramycin in cystic fibrosis patients. *Acta Otolaryngol.* 2009;129:4–7.
6. Prayle A, Smyth AR. Aminoglycoside use in cystic fibrosis: therapeutic strategies and toxicity. *Curr Opin Pulm Med.* 2010;16:604–610.
7. Smyth A, Tan KHV, Hyman-Taylor P, et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations in cystic fibrosis—the TOPIC study, a randomised controlled trial. *Lancet.* 2005;365:573–578.
8. Nakano S, Song J, Ogawa N. Chronopharmacokinetics of gentamicin: comparison between man and mice. *Ann Rev Chronopharmacol.* 1990;7: 277–280.
9. Yoshiyama Y, Grenier L, Gourde P, et al. Temporal variation in nephrotoxicity of low doses of isepamicin in rats. *Antimicrob Agents Chemother.* 1996;40:802–806.
10. Dickson CJ, Schwartzman MS, Bertino JS. Factors affecting aminoglycoside disposition: effects of circadian rhythm and dietary protein intake on gentamicin pharmacokinetics. *Clin Pharmacol Ther.* 1986;39:325–328.

11. Lucht F, Tigaud S, Esposito G, et al. Chronokinetic study of netilmicin in man. *Eur J Clin Pharmacol*. 1990;39:199–201.
12. Bleyzac N, Allard-Latour B, Laffont A, et al. Diurnal changes in the pharmacokinetic behavior of amikacin. *Ther Drug Monit*. 2000;22:307–312.
13. Elting L, Bodey GP, Rosenbaum B, et al. Circadian variation in serum amikacin levels. *J Clin Pharmacol*. 1990;30:798–801.
14. Prayle AP, Jain K, Touw DJ, et al. The pharmacokinetics and toxicity of morning vs. evening tobramycin dosing for pulmonary exacerbations of cystic fibrosis: a randomised comparison. *J Cyst Fibros*. 2016;15:510–517.
15. Beauchamp D, Labrecque G. Chronobiology and chronotoxicology of antibiotics and aminoglycosides. *Adv Drug Deliv Rev*. 2007;59:896–903.
16. Touw DJ, Knox AJ, Smyth A. Population pharmacokinetics of tobramycin administered thrice daily and once daily in children and adults with cystic fibrosis. *J Cystic Fibrosis*. 2007;6:327–333.
17. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolised recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med*. 1994;331:637–642.
18. Touw DJ, Vinks AA, Neef C. Pharmacokinetic modelling of intravenous tobramycin in adolescent and adult patients with cystic fibrosis using the nonparametric expectation maximization (NPEM) algorithm. *Pharm World Sci*. 1997;19:142–151.
19. Proost JH, Meijer DK. MW/Pharm, an integrated software package for drug dosage regimen calculation and therapeutic drug monitoring. *Comput Biol Med*. 1992;22:155–163.
20. Jelliffe RW. Estimation of creatinine clearance when urine cannot be collected. *Lancet*. 1971;1:975–6i.
21. De Broe ME, Giuliano RA, Verpooten GA. Choice of drug and dosage regimen. Two important risk factors for aminoglycoside nephrotoxicity. *Am J Med*. 1986;80:115–118.
22. Jelliffe RW, Iglesias T, Hurst AK, et al. Individualising gentamicin dosage regimens: a comparative review of selected models, data fitting methods and monitoring strategies. *Clin Pharmacokinet*. 1991;21:461–478.
23. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med*. 2002;30:536–540.
24. Vinks AA, Touw DJ, Heijerman HG, et al. Pharmacokinetics of ceftazidime in adult cystic fibrosis patients during continuous infusion and ambulatory treatment at home. *Ther Drug Monit*. 1994;16:341–348.
25. Singh RK, Singh Y, Srivastava R. Circadian variation of serum urea concentration in north Indian subjects. *Indian J Med Res*. 1990;92:257–259.
26. Prayle A, Watson A, Fortnum H, et al. Side effects of aminoglycosides on the kidney, ear and balance in cystic fibrosis. *Thorax*. 2010;65:654–658.
27. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–29.
28. Larsson A, Akerstedt T, Hansson LO, et al. Circadian variability of cystatin C, creatinine, and glomerular filtration rate (GFR) in healthy men during normal sleep and after an acute shift of sleep. *Chronobiol Int*. 2008;25:1047–1061.