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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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. The exclusion criteria were administration of other nephrotoxic drugs, allergy to aminoglycosides, pregnancy, granulocytopenia (<1.0 × 10⁹/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 CF and MW/Pharm pharmacokinetic software package version 3.60. 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, 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 χ² 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

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<th>TABLE 1. Baseline Characteristics of the 8:00 and 22:00 Groups</th>
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<td><strong>Time of Administration</strong></td>
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<tr>
<td>No. of patients</td>
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<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Male sex (%)</td>
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<tr>
<td>Weight (kg)</td>
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<td>Serum creatinine (mmol/mL)</td>
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<td>BUN (mmol/mL)</td>
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C15, creatinine clearance; C15, creatinine clearance; eGFR, 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.
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

| TABLE 2. Dosing and Pharmacokinetic Parameters Are Presented as Means or Medians With SDs or Ranges Given in Parentheses, Respectively |
|---|---|---|
| **Time of Administration** | **8:00** | **22:00** | **P** |
| **Day 1** | | | |
| Dose (mg) | 525 (420–600) | 500 (400–600) | 0.35† |
| Cl\(_{\text{TOB}}\) (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 (mg) | 500 (500–720) | 550 (400–640) | 0.39† |
| Cl\(_{\text{TOB}}\) (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\(_{\text{TOB}}\), clearance of tobramycin; Vd, volume of distribution.
*Student \( t \) test.
†Mann–Whitney \( U \) test.
‡Normalized to a tobramycin dose of 500 mg.

**FIGURE 1.** The graphs are box-and-whisker plots of tobramycin clearance (Cl\(_{\text{TOB}}\), A), volume of distribution (Vd, 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.
owing to an altered status of the immune system may also have been selected. Perhaps, the circadian rhythm in the urinary KIM-1 increase detected in children with CF may not be considered clinically relevant and is in line with the rapid renal clearance of tobramycin in patients with CF compared to patients with non-CF.

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.

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 mmol/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. Polycationic aminoglycosides such as tobramycin can alter glomerular ultrastructure, permeability, and reabsorption. 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, β2-microglobulin, and N-acetyl-β-glucosaminidase, throughout the day. 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. 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