Does the Circadian Rhythm affect the Pharmacokinetics of Tobramycin in Cystic Fibrosis patients?

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Abbreviations are: eGFR, glomular filtration rate estimated with C&G formula; BUN, blood urea nitrogen.

Objective
To investigate the effect of the circadian rhythm on the pharmacokinetics of tobramycin in adult CF patients.

Introduction
• High cumulative dosages of intravenous aminoglycosides are associated with increased rates of nephro- and ototoxicity.
• Once-daily-dosing of tobramycin (TOB) is at least as effective and may be less toxic compared to multiple daily dosing in patients with cystic fibrosis (CF).
• With the introduction of once-daily-dosing the timing of TOB dosing may be relevant, since rapid clearance of aminoglycosides is crucial to prevent renal toxicity.
• An effect of the circadian rhythm on renal clearance of aminoglycosides has been demonstrated in a general ward population and postulated in CF patients.
• Therefore, the effect of the circadian rhythm on the pharmacokinetics of TOB in adult CF patients was investigated.

Methods
The study was performed in an open randomized design. Patients with cystic fibrosis, treated for a pulmonary exacerbation with intravenous TOB at the Haga Teaching Hospital, The Netherlands were eligible for inclusion. After inclusion patients were randomised, receiving TOB either at 8:00 or at 22:00. After infusion a peak and a second level at 6-10 h after end of infusion of TOB were drawn at day 1 and day 8.

Clearance, volume of distribution and area-under-the-curve were calculated using a one-compartment model with linear pharmacokinetics. For comparison of baseline characteristics a Student’s T-test for variables with normal distribution and a two-tailed Mann–Whitney U test for nonparametric variables was used. For categorical variables we used a Chi-square test.

Pharmacokinetic parameters and biochemical parameters of renal function (GFR and BUN) were compared between groups using a Student’s t-test after log transformation. P-Values <0.05 were considered statistically significant.

Results
Twenty-four patients were included. No significant differences were found in patient characteristics between the two groups (Table 1). Median volumes of distribution were 0.25 and 0.26 L/kg (p=0.37) and median clearances were 5.7 and 5.3 ml/min (p=0.43) for the 8:00 and 22:00 group, respectively. After correction of TOB clearance for baseline creatinine clearance the effect of time of administration did not result in a statistically significant effect (p=0.19). No significant difference in pharmacokinetic parameters at day 8 compared to day 1 was detected (Figure 1). GFR and BUN did not differ significantly between the 2 groups at day 1 or day 8.

Table 1: Patient characteristics of 8:00 AM and 22:00 PM groups. Differences in categorical variables were expressed as numbers and percentages, and continuous variables as means if normally distributed and if not normally distributed as median.

Conclusions
Time of administration had no influence on the pharmacokinetics of TOB in CF patients. This could be contributed to a disturbance of the circadian rhythm during a pulmonary exacerbation. Consequently, an effect on treatment outcomes is unlikely.

Recommendations
A preferential time of administration of intravenous TOB can be chosen by the CF clinic based on practical considerations. It is, however, important to maintain a 24h-dosing interval in order to minimize toxicity without compromising efficacy.

References

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