

PHARMACOKINETICS OF ONCE-DAILY TOBRAMYCIN IN ADULT CYSTIC FIBROSIS PATIENTS.

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REVISED ABSTRACT

Background: Once-daily dosing (ODA) of aminoglycosides is now advocated due to ease of administration and improved toxicity profile. However, the optimal sampling times (OST) for this new dosing regimen have not been clearly established. A recent pharmacokinetic (PK) study in healthy volunteers demonstrated a prolonged distribution phase and reduced clearance using a 7mg/kg dose compared with the traditional 2 mg/kg dose (Demczak, Antimicrob. Agents Chemother., 1997; 41:1115-19). Due to the altered PK in patients with CF, the daily doses are administered (10-15 mg/kg). The purpose of this study is to evaluate the PK of once-daily tobramycin administration in CF patients. The specific objectives are to compare the distribution and elimination parameters of traditional (3.3mg/kg q8h) dosing versus high dose (10mg/kg q24h) tobramycin, and to determine the OST to facilitate dosage individualization in the clinical setting.

Methods: Six adult CF patients were enrolled in this prospective, crossover trial. Blood samples were obtained following a single dose of tobramycin 3.3mg/kg and 10mg/kg. Serum concentrations were fitted to a one- and two-compartment model (IT2B). OST were determined using ADAPT II.

Results: Analysis revealed the pharmacokinetic were best described using a two-compartment model (see tables).

Conclusions: Similar to the results of Demczak, the distribution phase for ODA appears to be longer than that of traditional dosing (TDA), though not statistically significant. Use of the above PK model and the OST provide a means for estimation of the parameters necessary for dosage individualization. If a 1-compartment model is employed, peak concentrations should be contained 2 and 3 hours after the end of the infusion (instead of the traditional one-half hour) to compensate for the prolonged distribution phase.

BACKGROUND

Tobramycin is a frequently prescribed antibiotic for the treatment of pneumonias in cystic fibrosis (CF) patients. It has potent bactericidal activity against the predominant pathogen in CF pneumonia, *Pseudomonas aeruginosa*. Recent studies suggest that administration of higher doses of tobramycin (10mg/kg) once daily may be as safe and effective as the traditional (3.3mg/kg) three times daily dosing. Currently, insufficient studies have been performed to evaluate potential differences in pharmacokinetic parameters between the two regimens.

OBJECTIVES

- Evaluate the pharmacokinetics of once-daily tobramycin administration in CF patients admitted for treatment of an acute exacerbation
- Compare the distribution and elimination patterns of traditional (3.3mg/kg q8h) dosing versus high dose (10mg/kg q24h) tobramycin
- Determine the optimal sampling strategy for monitoring of serum concentrations within the clinical setting

METHODS

- Prospective, crossover trial (n=6)
- Day 1: Tobramycin 3.3 mg/kg q8h over 30 minutes x3 doses
Blood samples drawn pre-infusion, immediately after, 10, 20, 30, 45, 60, 90, 120, 240, and 450 minutes after the first dose
- Day 2: Tobramycin 10mg/kg over 1 hour x1 dose
Blood samples drawn pre-infusion, immediately after, 10, 20, 30, 45, 60, 90, 120, 240, 450, and 720 minutes after the single dose

DATA ANALYSIS

- Study data fitted to both one and two-compartment pharmacokinetic models.
- Model discrimination determined by Akaike information criterion (AIC) and examination of the residual error.
- Pharmacokinetic parameters analyzed: volume of distribution, clearance, half-life (distribution and elimination).
- Optimal sampling times determined using ADAPT II software.

Table 1. Patient Demographics

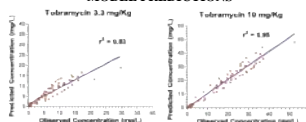
Parameter	Mean ± SD	Range
Males/Females	4/2	—
Age (yrs)	29.0 ± 4.6	23-34
Height (in)	65.5 ± 1.3	64-68
TBW (kg)	55.3 ± 13.8	45-75
BSA (m ²)	1.6 ± 0.2	1.47-1.87
CLcr (ml/min/1.73m ²)	127.0 ± 5.8	120.6-132.9
Low Dose (mg)	186.7 ± 42.7	140-240
High Dose (mg)	343.3 ± 138	440-740

Table 2. Pharmacokinetic Parameters for Low and High Dose Tobramycin

Parameter	Mean Parameter	Q8H	Q24H	P value
T ^{1/2} α (hr)	0.65	0.91	0.28	
T ^{1/2} β (hr)	3.58	2.72	0.08	
Vc (l/kg)	0.19	0.21	0.24	
Vss (l/kg)	0.36	0.29	0.08	
CLd (l/hr/1.73m ²)	6.55	5.64	0.18	
CLr (l/hr/1.73m ²)	4.08	2.41	0.43	
AUC _{0-∞} (mg-h/L)	98.9	100.4	0.85	
Optimal sampling times (hr)	0.5, 8	1, 15, 5		

Vc=volume of central compartment, Vss=steady-state volume, AUC=area under the curve, CLd=total clearance, CLd=distribution clearance

MODEL PREDICTIONS

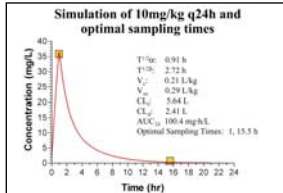
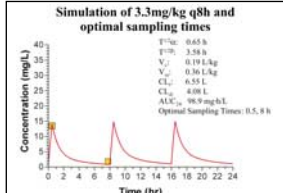


COMPARATIVE PHARMACOKINETICS

	CL (L/hr/Kg)	Vd (L/Kg)	P
	Q8H	Q8H	QD
Gagliardo et al	0.10	0.10	0.26 0.26 NS
Bates et al	0.11	0.12	0.26 0.26 NS
Current	0.11	0.10	0.36 0.29 NS

RESULTS

- The serum concentration-time curves were best described using a two-compartment model.
- The volume of distribution and clearance values in each dosing group are consistent with those previously reported.
- The distribution and elimination patterns were not significantly different between the tobramycin once-daily and traditional dosing groups.
- Distribution half-lives were more prolonged than expected in both dosing groups requiring peak sampling at 2 and 3 hours with traditional and once-daily dosing groups respectively using a one-compartment model.



CONCLUSIONS

- No dose dependent pharmacokinetic differences were evident when comparing traditional and once-daily tobramycin dosing in patients with CF.
- A two compartment model is preferable for therapeutic drug monitoring of tobramycin. Peak concentrations should be obtained at the end of infusion for traditional and once daily dosing respectively.
- A one-compartment pk model should be used cautiously due to the prolonged distribution phase. Peak concentrations should be obtained 2 and 3 hours after infusion of traditional and once daily dosing respectively.

REFERENCES

- Gagliardo L, Quen L, Sordani MS. Pharmacokinetics of once daily vs three daily tobramycin in patients. JAC 1992;37:1040-4.
 Bates RD, Nelson MC, Bates PR, et al. Pharmacokinetics and safety of tobramycin after once-daily administration in patients with CF. Chest 1997;112:130-3.
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