



# ARE WE OVERDOSING PATIENTS RECEIVING CONCURRENT INTRAVENOUS AND INHALED TOBRAMYCIN?

Megan J. Montgomery, Pharm.D.<sup>1</sup>, Paul M. Beringer, Pharm.D.<sup>1</sup>, Mark A. Gill, Pharm.D.<sup>1</sup>, Stan G. Louie, Pharm. D.<sup>1,2</sup>, and Bertrand Shapiro, M.D.<sup>2</sup>  
 School of Pharmacy<sup>1</sup>, School of Medicine<sup>2</sup>, University of Southern California, Los Angeles, CA



## ABSTRACT

**PURPOSE:** Inhaled tobramycin (IHT) improves pulmonary function and reduces hospitalization in cystic fibrosis (CF) patients over a 28-day cycle. A regimen containing intravenous tobramycin (IVT) concurrently is often prescribed to treat acute pulmonary exacerbations. However, IHT significantly affects the serum concentrations of IVT and define appropriate dosing and monitoring strategies. **METHODS:** Tobramycin serum concentrations from 30 adult CF patients were modeled using a pharmacokinetic (PK) model based on data from a 3.3 mg/kg q8h and 16mg/kg qd Monte Carlo simulation. The model was used to predict the effects of 1) simultaneous administration of IHT and IVT, 2) IHT given 1 hour prior to IVT and 3) IHT given 4 hours prior to IVT on serum concentrations of IVT. Drug levels were calculated to evaluate the bias that concurrent IHT administration would have on peak and trough levels and AUC. The effect on serum concentrations of IVT. Drug levels should be obtained when IHT is given separate from the IVT dose. If IHT and IVT are administered concurrently, the intravenous dose should be decreased by 15%.

## INTRODUCTION

Tobramycin for inhalation (TOBI®) is approved for chronic maintenance therapy in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*.  
 • Improves pulmonary function  
 • Inhalation delivers high concentrations of antibiotic directly to the airways, with minimal systemic absorption and toxicity.  
 • Currently, there is no data to support the use of TOBI® for treatment of acute pulmonary exacerbations, however, some CF centers continue TOBI® in combination with intravenous tobramycin during hospitalizations if during the 28-day on cycle.  
 • Recently this practice has been discouraged due to concerns for the development and spread of resistance in the hospital setting.

## STUDY OBJECTIVES

- Evaluate whether inhaled tobramycin significantly affects the serum concentrations of intravenous tobramycin.
- Define appropriate dosing and monitoring strategies.

## METHODS: INTRAVENOUS AND INHALED TOBRAMYCIN SIMULATIONS

- **Intravenous tobramycin (IVT):**
  - Serum tobramycin concentrations from 30 adult CF patients were fitted to a 1-compartment model using MAP Bayesian analysis. A priori PK parameters that were previously published were used.
  - Steady-state serum tobramycin concentrations were then simulated based on doses of (Adapt ID):
    - 3.3 mg/kg per day
    - 4.3 mg/kg every 8 hours
- **Inhaled tobramycin (IHT):**
  - Adapt ID simulation (Adapt ID) was performed to generate 30 sets of PK parameters based on parameter estimates from a published PK study.
  - IHT PK parameters, mean (standard error):
    - $V_d$ : 125 (6.75)  $V_d$ : 812 (10.4)
    - $Cl$ : 125 (6.75)  $V_d$ : 490 (133)
  - Steady-state serum tobramycin concentrations were then simulated for the normal dose of 500mg twice daily (Adapt ID).

## METHODS: SIMULATION OF IHT AND IVT

- **IVT + IHT**
  - Simulations were performed to model the following effects at the time of sampling:
    - Simultaneous administration of IHT and IVT
    - IHT given 1 hour prior to IVT
    - IHT given 4 hours prior to IVT
  - For the q8h regimen, peak and trough levels were predicted for the 5<sup>th</sup> dose.
  - For the qd regimen, peak and trough levels were predicted for the 3<sup>rd</sup> dose.
- Simulated peak and trough levels of IHT + IVT were used to generate revised PK parameters (USC\*PACK).

## METHODS: DATA ANALYSIS

- Predictive performance evaluation<sup>5</sup>
  - Bias: median prediction errors (PE)
  - PE = predicted - true = (IHT + IVT) - IVT
  - %PE =  $\frac{(IHT + IVT) - IVT}{IVT} \times 100$

## RESULTS: PATIENT DEMOGRAPHICS

Characteristic	Mean ± S.D.	Range
Age (yr)	28 ± 5.9	21-43
Male/female (n)	18/12	
Height (inches)	66.1 ± 2.9	58-74
Weight (kg)	54.4 ± 9.6	33-72
Lean Body Mass (kg)	44.5 ± 6.3	27.9-56.8
CL <sub>cr</sub> (ml/min/1.73m <sup>2</sup> )	124.1 ± 23.6	87-182

Lean body mass calculated according to Hallyneck et al.  
 CL<sub>cr</sub> calculated according to Jelliffe and Jelliffe.

## RESULTS: IVT PK PARAMETERS

PK parameter	Median (Range)
V <sub>d</sub> (L/kg)	0.32 (0.18-0.74)
Cl <sub>t</sub> (L/kg/h)	0.09 (0.06-0.17)
k <sub>e1</sub> (h <sup>-1</sup> )	0.26 (0.12-0.39)
T <sub>1/2</sub> (h)	2.71 (1.80-5.63)

## RESULTS: PEAK/TROUGH LEVELS

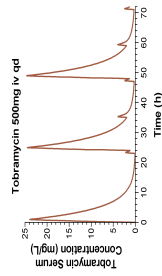
Regimen	Median Peak (mg/L)	Median Trough (mg/L)	Peak PE (%)	Trough PE (%)
3.3 mg/kg Q8H	10.71	1.46	1.33 (15.97%)	0.16 (0.55%)
IHT 1 hour before	10.38	3.96	1.06 (10.60%)	1.78 (14.488%)
IHT 4 hours before	10.97	1.07	0.31 (4.51%)	0.66 (5.77%)
IHT simultaneous	21.09	0.39	1.07 (4.84%)	0.16 (21.69%)
IHT 1 hour before	20.82	1.93	0.76 (3.49%)	1.78 (5.63.07%)
IHT 4 hours before	20.64	0.77	0.43 (1.94%)	0.66 (7.788%)

## RESULTS: PK PARAMETERS

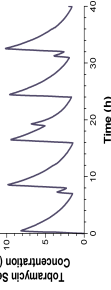
Regimen	Kd (h <sup>-1</sup> )	Median (PE%)	T <sub>1/2</sub> (h)	AUC <sub>0-24</sub> (mg·h/L)
3.3mg/kg Q8H	0.26 (2.6%)	0.29 (10.4%)	2.65 (97.5%)	131.20 (31.20%)
IHT 1 hr before	0.16 (-42.0%)	0.38 (15.21%)	4.30 (95.70%)	169.69 (69.69%)
IHT 4 hr before	0.22 (-15.6%)	0.33 (2.74%)	3.13 (96.87%)	132.09 (32.09%)
IHT simultaneous	0.23 (5.77%)	0.31 (2.76%)	3.02 (96.98%)	132.56 (32.56%)
IHT 1 hr before	0.11 (-61.70%)	0.40 (27.85%)	6.36 (95.68%)	233.48 (123.48%)
IHT 4 hr before	0.16 (-38.31%)	0.37 (10.75%)	4.32 (95.68%)	178.01 (78.01%)

## RESULTS: SIMULATION OF IHT ADMINISTERED 1 HOUR BEFORE IVT

Tobramycin 500mg iv qd

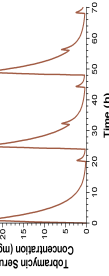


Tobramycin 160mg iv q8h

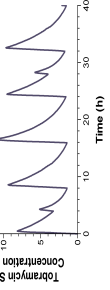


## RESULTS: SIMULATION OF IHT ADMINISTERED 4 HOUR BEFORE IVT

Tobramycin 500mg iv qd



Tobramycin 160mg iv q8h



## RESULTS: AUC's

- The median AUC<sub>IHT</sub> is 17.99 mg•h/L.
- The median AUC<sub>IVT</sub> for q8h and qd is 108.64 mg•h/L and 110.07 mg•h/L, respectively.
- The median AUC<sub>IHT</sub> is 14.7% of the AUC<sub>IVT</sub>.

## CONCLUSIONS

In addition to concerns regarding the development and spread of resistance, the administration of IHT concurrently with IVT has a time-dependent effect on the serum concentrations of tobramycin and adds to the overall exposure.

- If administered concomitantly with IVT, TOBI® should be administered at least 4 hours prior to the IVT dose at which peak and trough levels (or random levels for QD dosing) are obtained.
- If IHT and IVT are administered concomitantly, the intravenous dose should be decreased by 15%.

## REFERENCES

1. Prober CG, et al. Pediatrics. 2000;106(6):1-6.
2. Beringer PM, et al. Antimicrob Agents Chemother. 2000;44(4):809-813.
3. Touw DJ, et al. Pharm World Sci. 1997;19:142-151
4. Phitick WH, et al. Pharmacokinetics and bioavailability of aerosolized tobramycin (TOBI®). Presented at the North American Cystic Fibrosis Conference, October 1999, Seattle, WA.
5. Shetler L, and Beal S. J Pharmacokinetic Biopharm. 1981;9(4):503-12.