Tobramycin Absorption and Retention in the Rat Lung following Airway Administration
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Purpose
To understand tobramycin’s lung disposition after airway administration. This polycationic aminoglycoside antibiotic, inhaled twice daily via nebulizer, is thought responsible for significant improvements in the health of CF patients with pulmonary infections of Pseudomonas aeruginosa.

Methods
A realistic ex vivo model, the isolated perfused rat lung, IPRL, was used to investigate the drug’s behavior at typical therapeutic concentrations. Tobramycin at different nominal doses was administered in aqueous solution to the airways. The mean fraction of each administered dose reaching the perfusate, Fp, was compared to that of the absorption markers, fluorescein and mannitol, as a function of time following administration. Dynamic dialysis was used to confirm and quantify tobramycin binding to lung tissue after slicing the IPRL immediately after drug administration. Data were analyzed for absorption and lung binding, to explore the kinetics and mechanisms responsible for the antibiotic’s pulmonary disposition.

Results
Unlike the absorption markers fluorescein and mannitol, that both showed monoexponential dose-independent increases in Fp with time, tobramycin’s pulmonary absorption in the IPRL was bi-exponential and dose-dependent due to tissue binding. Best estimates for the first-order rate constants of tobramycin absorption (ka) appeared dose-independent (0.069-0.071 min⁻¹), with values close to the mean for fluorescein (0.076 min⁻¹). The rate constant for dissociation from IPRL tissue (k21) was also relatively constant (0.021-0.022 min⁻¹), while that for association (k12) decreased from 0.20 to 0.07 min⁻¹ with increasing airway dose from 0.002 to 2 mg. Tobramycin binding to the lung was confirmed by independent dynamic dialysis studies that confirmed the existence of a “slow on, slow off” type of behavior. While the exposure of drug to some additional tissue sites was possible due to the slicing involved in the dialysis experiments, the data trends seen with dialysis were consistent with those seen in the intact IPRL.

Conclusion
Tobramycin absorption appeared quite fast following administration to the airways of the IPRL while dose-, and concentration-, dependent slow onset tissue binding appears to extend the duration of tobramycin presence in the lung. This may be one explanation for the apparent success of tobramycin therapy when treating pulmonary infections.

Figure 1: Mean (±SD) fraction of administered dose, D, transferred to perfusate vs time for fluorescein (nominal dose = 0.02 mg; open symbols) and tobramycin (closed symbols). Key: Nominal doses were 0.002 mg (●; n=6); 0.02 mg (○; n=5); 0.2 mg (▲; n=5) and 2 mg (●; n=4). Solid curves are the best fits for all profiles.

Figure 2: Mean fraction of remaining tobramycin in the sac vs. time. Error bars are sample standard deviations (n=3). Key: ●: 0.002 mg; ▲: 0.004 mg; ○: 0.2 mg; ■: 2 mg; ■: 10 mg; ▲: control. Dotted lines are the best fitted curves using the models.