Biopharmaceutical Characterization of Nebulized Antimicrobial Agents in Rats: 3. Tobramycin

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The aim of this study was to determine the biopharmaceutical characteristics of tobramycin (TOB) after nebulization in rats. TOB was administered by intravenous (i.v.) bolus or intratracheal nebulization (3 mg · kg⁻¹), and concentrations were determined in plasma and epithelial lining fluid (ELF) by liquid chromatography-tandem mass spectrometry. The ratio of the TOB concentration in ELF to the plasma area under the curve (AUC) was more than 200 times as high after NEB as after i.v. bolus administration, indicating that TOB nebulization offers a biopharmaceutical advantage over i.v. administration.

Much higher intrapulmonary antibiotic concentrations may be achieved after nebulization (NEB) than after systemic administration, which may be of value for the treatment of pulmonary infections (1). However, this potential advantage may vary between compounds and could be much greater for antibiotics with a weak rather than a strong ability to permeate membranes, as recently shown for colistin (2) in comparison with ciprofloxacin or moxifloxacin (3). The aim of this study was to confirm this hypothesis by investigating the pulmonary pharmacokinetics (PK) of tobramycin (TOB), another antibiotic with a weak ability to permeate membranes that is clinically available for pulmonary infections (1). However, this potential advantage may vary with an X bridge C18 column (5.0 mm [inside diameter]; Waters, St-Quentin en Yvelines, France) used for statistical comparisons.

Using Calu-3, the highest TOB concentrations (250 and 2,500 µg · ml⁻¹) applied to the apical side of monolayers, the TOB concentrations on the basal side were below the limit of quantification (2.5 ng · ml⁻¹), meaning that the $P_{app}$ of TOB concentrations in epithelial lining fluid ($C_{ELF}$) were derived from measured TOB concentrations in BAL fluid ($C_{BAL}$) after correction by urea dilution (7). TOB concentrations in plasma and ELF versus time were simultaneously analyzed by a nonlinear mixed-effects method with S-ADAPT software (v 1.52), and the final structural PK model was derived from previous studies (2, 3).

One or two compartments were assessed to describe TOB PK in plasma, but the one-compartment model was kept. TOB PK in ELF were first tested with one ELF compartment with a fixed physiological volume ($V_{ELF} = 30$ µl · kg⁻¹) as previously described (2, 3) and with the addition of a depot compartment (2), but two compartments with distinct volumes ($V_{ELF1}$, $V_{ELF2}$) were necessary to reflect the previously described complexity of ELF PK (8). In the final model, compartments were connected by two-direction equilibrium distribution clearances, but the addition of an influx clearance from the ELF1 compartment to the central compartment was necessary for satisfactory data fitting. Systemic bioavailability after NEB was fixed at its maximum value (100%). Areas under the plasma and ELF concentration-versus-time curves from zero to infinity (AUCplasma, AUCELF) were calculated from the model. Elimination half-lives ($t_{1/2\text{plasma}}$ and $t_{1/2\text{ELF}}$) after intravenous (i.v.) administration and NEB were derived from the model. Prism5 (GraphPad, La Jolla, CA) was used for statistical comparisons.

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TOB should be $<0.05.10^{-6}$ cm$\cdot$s$^{-1}$. In vivo, rapid appearance of TOB in plasma was observed after NEB with an early concentration peak at 0.25 h, corresponding to the first sampling time (Fig. 1). These initial plasma drug concentrations were not significantly different ($P > 0.05$; Mann-Whitney test) after NEB and i.v. administrations ($5.45 \pm 0.90$ versus $4.89 \pm 0.70$ µg$\cdot$ml$^{-1}$). Elimination half-lives in plasma were virtually identical after NEB and i.v. administrations ($t_{1/2plasma,NEB} = 0.57$ h; $t_{1/2plasma,i.v.} = 0.53$ h). Notably, the $t_{1/2}$ in ELF after NEB ($t_{1/2ELF,NEB} = 0.92$ h) was slightly longer than that in plasma (Fig. 1) for unexplained reasons that required a model with two ELF compartments. Interestingly, the TOB concentrations at distribution equilibrium (2.5 and 4 h) were approximately 250 times as high in ELF after NEB than after i.v. administration (Fig. 1). Accordingly, the AUC in ELF was 242 times as high after NEB as after i.v. administration ($\text{AUCELFL,NEB} = 1,212$ µg$\cdot$h$\cdot$ml$^{-1}$ versus $\text{AUCELFL,i.v.} = 5.1$ µg$\cdot$h$\cdot$ml$^{-1}$). This effect of the route of administration may also be assessed by comparing the ELF-to-plasma AUC ratio after NEB ($\text{AUCELFL,NEB}/\text{AUCELFL,i.v.} = 222$) with that after i.v. administration ($\text{AUCELFL,i.v.}/\text{AUCELFL,i.v.} = 0.97$). Together, these data show that, at least under these experimental conditions, the route of administration has a major effect on TOB concentrations within ELF, as was previously observed with colistin (2). TOB is a smaller molecule than colistin (respective molecular masses, 467.5 and 1,166 g$\cdot$mol$^{-1}$) but has a log P value close to that of colistin (respectively, $-6.5$ and $-8.1$) (ChemaAxon, www.drugbank.ca) and a weak apparent ability to permeate membranes ($<0.05.10^{-6}$ cm$\cdot$s$^{-1}$), like that of colistin (2) but much weaker than those of fluoroquinolones ($0.8 \pm 0.03.10^{-6}$ cm$\cdot$s$^{-1}$ for ciprofloxacin and $8.3 \pm 0.12.10^{-6}$ cm$\cdot$s$^{-1}$ for moxifloxacin) (3).

In conclusion, this study has confirmed that, as for colistin, TOB NEB offers a biopharmaceutical advantage by achieving high ELF and low systemic concentrations, consistent with its limited ability to permeate membranes.

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REFERENCES