High *In Vivo* Amikacin Lung Deposition After NKTR-061 Dosing Correlates With *In Vitro* Aerosol Characterization

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Abstract

Introduction: NKTR-061 is a proprietary aerosolization system for amikacin (AMK) optimized for use in mechanically ventilated patients (MVP). In Phase II development, NKTR-061 is being studied as an adjunct to IV antibiotic therapy for pneumonia. In MVP with pneumonia, Niederman *et al*. reported peak tracheal aspirate AMK concentrations of 16,212 µg/mL ± 3,675 after NKTR-061 administration[1] as compared to bronchial secretion concentrations of 14 µg/mL ± 4.2 after 15 mg/kg IV administration[2] confirming highly efficient delivery of AMK in the intensive care setting. This report describes *in vitro* and *in vivo* characterization of a hand-held version, intended for use in extubated patients. **Methods:** Using an *in vitro* model simulating adult tidal breathing (VT 500 mL, RR of 15 bpm, PIFR of 32 L/min, and I:E of 1:1.7; n=9), NKTR-061 (AMK 400 mg) was aerosolized continuously and the emitted mass captured on absolute filters distal to the mouthpiece. *In vivo*, NKTR-061 (400 mg AMK) labeled with 99mTc was administered to healthy subjects using the hand-held version, with drug deposition and distribution determined via scintigraphy. **Results:** *In vitro*, the emitted mass was 87% of the 400 mg AMK nominal dose, with a predicted lung dose of 45-50% calculated as the emitted mass times the FPF < 5 µm†. *In vivo*, mean AMK lung dose determined via scintigraphy was 172.2 mg, 43% of the nominal dose. Lung doses in this range are expected to achieve peak lung AMK concentrations that are several times greater than the minimum inhibitory concentration (MIC) of Gram-negative microorganisms commonly associated with pneumonia in MVPs. In contrast, conventional hand-held nebulizers[3] or IV administration of AMK[4] result in only 5-10% of the dose reaching the lungs, limiting the likelihood of achieving concentrations required for bacterial eradication of several times more than the MIC. **Conclusions:** The hand-held version of NKTR-061 delivered a large fraction of the starting dose, confirming the high delivery efficiency predicted by *in vitro* aerosol characterization. Lung doses in the range of those observed are expected to achieve bacteriological eradication.

Introduction

- Amikacin is a well-known aminoglycoside antibiotic typically administered intravenously for the treatment of infections caused by Gram-negative bacteria.
- The spectrum of activity of amikacin makes it suitable for use in patients with nosocomial pneumonia.[5]
- Several reports describe the use of aerosolized antibiotic, such as amikacin, as adjunctive therapy for patients with deep lung infections – specifically Gram-negative pneumonia.[6]
- Aerosolized therapies may minimize systemic drug exposure while delivering the drug directly to the site of infection.
- However, aerosolized antibiotic therapy has been hampered by the low efficiency of pulmonary drug delivery when using conventional hand-held nebulizers.[3]
- This study reports on the *in vitro* and *in vivo* efficiency of the hand-held version of a proprietary high-efficiency nebulizer system called the Pulmonary Drug Delivery System (PDDS Clinical) to administer aerosolized amikacin.
- The administration system is designed to use the same nebulizer/reservoir and volume of drug to deposit similar amounts of drug to the lungs of patients during both mechanical and spontaneous ventilation.
- Aerosolized amikacin administered via the PDDS Clinical hand-held device may increase efficacy and limit adverse effects due to systemic exposure by achieving high local concentrations while minimizing systemic absorption.

Objectives

In Vitro Study

- To characterize the amount of amikacin emitted distal to the PDDS Clinical hand-held device during simulated adult tidal breathing.
- To test robustness of the *in vitro* model by comparing the *in vitro* inhaled mass with *in vivo* inhaled mass quantified by scintigraphy.

In Vivo Study – Healthy Volunteers

- To use gamma scintigraphy to measure the bronchopulmonary distribution of amikacin administered via the PDDS Clinical hand-held device to healthy subjects.
- To characterize the drug deposition and distribution associated with amikacin administered via the PDDS Clinical hand-held device.

† *FPF = fine particle fraction*

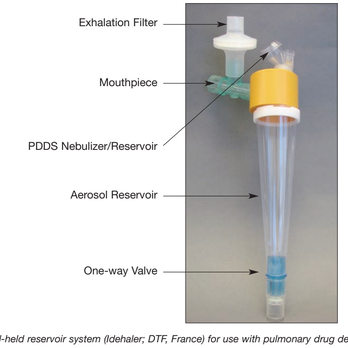

Figure 1: Hand-held reservoir system (Idehaler; DTF, France) for use with pulmonary drug delivery system nebulizer.

Materials and Methods

In Vitro Simulation

- AMK 400 mg (3.2 mL) was aerosolized continuously using the PDDS Clinical hand-held device with a mouthpiece generating an average particle size of 3.8 µm ± 0.2. Particle sizes in this range are reported in the literature as optimal for airway drug delivery.[7]
- Adult tidal breathing was simulated with a tidal volume of 500 mL, respiratory rate of 15 breaths/minute, peak inspiratory flow rate of 32 liters/minute and an inspiratory:expiratory ratio of 1:1.7.
- The emitted mass distal to the mouthpiece was captured on filters.
- Figure 2 depicts the resting adult breathing simulation.

Healthy Volunteers

- In this open-label study, healthy subjects received a single 400 mg (3.2mL) dose of aerosolized amikacin containing ^{99m}technitium (^{99m}Tc) administered using the PDDS Clinical hand-held device with a mouthpiece.
- Gamma scintigraphy was performed immediately following completion of the single dose of aerosolized amikacin.
- Figure 3 depicts the healthy volunteers undergoing scintigraphy.

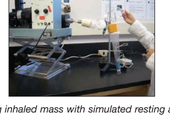

Figure 2: In vitro test setup for determining inhaled mass with simulated resting adult breathing patterns.

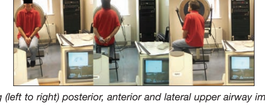

Figure 3: Scintigraphy scanning (left to right) posterior, anterior and lateral upper airway imaging.

Results

In Vitro

- The mean *in vitro* inhaled mass captured on a filter distal to the mouthpiece was 87% (± 2%) of the nominal 400 mg dose.
- The predicted lung dose (i.e., the amount of inhaled mass being deposited in the lung) was calculated using emitted mass times the FPF<5.0 µm and found to be 45-50% of the nominal dose.

Healthy Volunteers

- Table 1 reports the demographics of the 15 healthy volunteers.
- As measured by scintigraphy:
  - The mean *in vivo* inhaled mass (i.e., the sum of percent deposited in lungs, oropharynx, and exhaled air) was 84% (± ~5%) of the nominal 400 mg dose.
  - The lung dose (i.e., the amount of inhaled mass being deposited in the lung) was 43.1% (± 6.1).
  - Table 2 reports the deposition of drug for all subjects while the mean (± SD) percentage deposition of the nominal radio-labeled dose after inhalation was as follows:
    - Lung 43.1% (± 6.1)
    - Oropharynx 29.4% (± 7.4)
    - Remaining in device 16.1% (± 4.8)
    - Exhaled air 11.5% (± 5.5)
- Figure 4 depicts consistent and well-distributed deposition of the nominal radio-labeled dose among subjects after inhalation of amikacin.

Subject†	Age	Sex	Height (cm)	Weight (kg)	BMI (kg/m²)
0001	45	M	175.0	75.8	24.8
0002	58	M	177.0	70.6	22.5
0003	38	M	180.0	75.8	23.4
0004	53	M	182.0	82.2	24.8
0005	56	F	162.0	70.0	26.7
0007	23	M	178.0	75.0	23.7
0008	53	M	165.5	69.3	25.3
0009	54	M	169.0	78.7	27.6
0010	44	M	175.0	81.0	26.4
0011	39	M	171.0	71.6	24.5
0012	36	M	191.0	97.6	26.8
0013	63	F	153.0	66.3	28.3
0015	40	M	179.0	86.2	26.9

Table 1: Demographic data for healthy volunteers.

Subject†	Lung	Oral	Device	Exhaled
0001	39.6	36.1	13.5	10.7
0002	38.5	34.2	20.4	6.8
0003	47.7	24.5	17.4	10.4
0004	43.4	28.0	13.8	14.8
0005	33.6	37.9	10.2	18.3
0007	34.4	32.0	23.5	10.0
0008	41.2	34.0	17.8	7.0
0009	50.1	18.0	6.9	25.0
0010	43.2	31.5	17.7	7.6
0011	45.4	26.2	18.2	10.2
0012	55.6	14.5	21.3	8.5
0013	40.9	26.6	17.4	15.1
0015	45.9	38.4	10.6	5.1

Table 2: Deposition, according to anatomical location, of AMK 400 mg dose expressed in percentage for each subject.

†Subjects 0006 and 0014 were excluded from the summary statistics due to an unrelated AE and a possible poor inhalation technique, which resulted in approximately 50% of the dose remaining in the holding chamber of the PDDS Clinical hand-held.

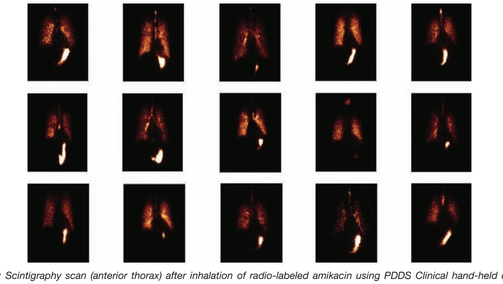

Figure 4: Scintigraphy scan (anterior thorax) after inhalation of radio-labeled amikacin using PDDS Clinical hand-held device in 15 healthy subjects.

Discussion

In Vitro

- The inhaled mass (i.e., the percentage of drug exiting the mouthpiece recovered on the filter) was 87% of the nominal dose, indicating excellent efficiency of the PDDS Clinical hand-held device.
- The predicted lung dose was 45-50% of the nominal dose.
- The *in vitro* model was predictive of the inhaled drug delivered *in vivo* with the PDDS Clinical hand-held nebulizer device.
- This suggests that the *in vitro* model is sufficient to identify effects of device design changes on clinical performance.

Healthy Volunteers

- The inhaled mass *in vivo* was 84% of the nominal dose.
- On average, 43% of the 400 mg inhaled amikacin dose was delivered to the lungs by the PDDS Clinical hand-held device. Under normal conditions of ventilation, standard pneumatic nebulizers deliver less than 10% of the nominal dose to the patient's lungs.[3,8]
- Scintigraphy results confirm that aerosolized amikacin is deposited consistently in the lung after inhalation through the PDDS Clinical hand-held device.

Conclusions

- The hand-held version of NKTR-061 for non-intubated patients delivers a large fraction of the starting dose to the lungs *in vivo*, confirming the high delivery efficiency predicted by *in vitro* aerosol characterization.
- This highly efficient delivery of NKTR-061 has also been confirmed in the intensive care setting in mechanically ventilated patients.[9]
- Lung doses in the range of those observed, whether in simulated *in vitro* experiments or measured *in vivo* in healthy subjects or MVPs, far exceed those delivered by conventional nebulizers and are expected to achieve bacteriological eradication.

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