Evidence of High Amikacin Lung Deposition in Mechanically Ventilated Patients (MVP) with Pneumonia and Healthy Subjects (HS) Dosed Using NKTR-061

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Abstract

Introduction: Intravenous (IV) antibiotics (AB) are 50-60% effective in treating pneumonia (PN) in MVP, thus PN results in significant morbidity and mortality.[1] AB inhalation delivers larger lung doses to the lung than IV but is problematic in MVP due to low lung deposition.[2] NKTR-061, a proprietary amikacin (AMK) aerosolization system optimized for ventilator circuits, is in clinical development as an adjunct to IV AB therapy for the treatment of PN. **Methods:** In a double-blind, placebo-controlled, Phase II study, MVP received 400 mg q24h (n=24) or q12h (n=21) for 7-14 days. Serial serum, tracheal aspirate (TA), and urine samples were collected on Day 3. Clinical parameters such as clinical pulmonary infection score (CPIS), days-on-ventilator, and IV AB use were monitored. In a separate study, healthy subjects (HS) without intubation (n=14) inhaled a single Technicium 99m-labeled 400 mg dose of AMK. Serum and urine were collected for 72 hours and lung and body deposition was determined with gamma scintigraphy. **Results:** Results are reported for the single 400 mg inhaled dose and the single 400 mg IV dose in HS and for the 400 mg q12h regimen in MVP (n=21). Mean AMK lung deposition was 112 mg and 172 mg in MVP and HS, respectively, with the difference arising from loss of drug in the ventilator circuit.† In MVP, peak AMK concentration in TA after NKTR-061 was 16,212 ±3,675 µg/mL versus 14 ±4.2 µg/mL after an IV dose of 15 mg/kg/day[3] while corresponding peak serum concentration of AMK after NKTR-061 was 3.2 ±0.5 µg/mL versus 47 ±4.2 µg/mL after IV administration. NKTR-061 caused a significant (p=0.02) dose-dependent reduction in IV AB use, with MVP dosed q12h requiring half as much concurrent IV AB after 7 days of treatment as those receiving placebo.[4] **Conclusions:** NKTR-061 achieves AMK lung exposures in MVP orders of magnitude greater than those after IV dosing. Greater target organ exposure with lower overall AMK doses and a reduction in serum exposure and concomitant AB use is expected to increase efficacy, reduce the incidence of AB resistance, and limit systemic AB toxicity.

† Lung dose in MVP was modeled using pharmacokinetic data from serum, urine, and tracheal aspirates.

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 ventilated patients with deep lung infections – specifically, Gram-negative pneumonia.[6]
- Such aerosolized therapies may minimize systemic drug exposure while delivering the drug directly to the site of infection.
- However, aerosolized AB therapy has been hampered by the low efficiency of pulmonary drug delivery when using conventional nebulizers connected to ventilator circuits.[2]
- This study reports pharmacokinetic and safety results of an investigational aerosolized amikacin, using a proprietary high-efficiency nebulizer system called the Pulmonary Drug Delivery System (PDDS Clinical), in both mechanically ventilated patients with pneumonia and in healthy subjects.
- Aerosolized amikacin administered via the PDDS Clinical may increase efficacy and limit adverse effects due to systemic exposure by achieving high local concentrations while minimizing systemic absorption.

Objectives

Healthy Volunteers

- To use gamma scintigraphy to measure the bronchopulmonary distribution of amikacin administered via the PDDS Clinical handheld device to healthy subjects.
- To describe the pharmacokinetics (PK) of a single dose of amikacin administered via the PDDS Clinical handheld and a single intravenous (IV) dose.

MVP with Pneumonia

- To evaluate aerosolized amikacin with respect to pharmacokinetic parameters, for use in conjunction with standard IV AB for the treatment of MVP with Gram-negative pneumonia.
- To assess the safety and tolerability of aerosolized amikacin in MVP with Gram-negative pneumonia.

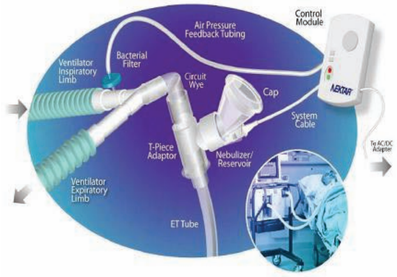

Figure 1: Diagram illustrating the unique pulmonary drug delivery system (PDDS Clinical).

Materials and Methods

Healthy Volunteers

- In this open-label, cross-over study, healthy subjects received a single dose of aerosolized amikacin containing ^{99m}technitium (^{99m}Tc) administered using the PDDS Clinical handheld device with a mouthpiece followed by a one-week washout period. Pharmacokinetic blood samples were collected before and after, and urine samples were collected for up to 72 hours.
- Gamma scintigraphy was performed immediately following completion of the single dose of aerosolized amikacin.
- During the second cross-over period, subjects received a single IV dose of commercially available amikacin sulfate solution. Pharmacokinetic blood samples were collected before and after, and urine samples were collected for up to 72 hours.

MVP with Gram-negative Pneumonia

- This study was a multi-center, randomized, double-blind, placebo-controlled, Phase II, dose-ranging clinical study to select the appropriate dose for pivotal trials of aerosolized amikacin in MVP with Gram-negative pneumonia. Reported herein are the pharmacokinetic results from patients who received the 400 mg q12 h dosing regimen.

MVP Key Inclusion Criteria	MVP Key Exclusion Criteria
18 years of age or older	Lung cancer, cystic fibrosis, active tuberculosis
Remain intubated and mechanically ventilated for 3 days	Immunocompromised
Clinical diagnosis of: ventilator-associated pneumonia > 48 hours after intubation, or hospital-associated pneumonia > 48 hours after admission, or health care facility-associated pneumonia	Severe hypoxemia
Clinical pulmonary infection score ≥ 6	Serum creatinine more than 2 mg/dL
Presence of Gram-negative organism by Gram-stain or culture	Hypersensitivity to aminoglycoside

Table 1: Key inclusion exclusion criteria for MVP.

Results

Healthy Volunteers

- Figure 2 depicts well-distributed deposition of the nominal radio-labeled dose in a representative healthy subject after inhalation of amikacin.
- Figure 3 depicts observed serum amikacin and predicted lung amikacin concentration-time profiles after administration of aerosolized amikacin to healthy subjects (left panel). For comparison, observed serum and bronchial secretion amikacin concentration-time profiles after IV administration to MVP as reported by Santré *et al* are depicted in the right panel. Aerosolized amikacin delivers high concentrations of drug to the lung with minimal systemic exposure compared to systemically delivered drug.
- 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)
- Table 2 shows the pharmacokinetic results after the inhaled dose of amikacin and the IV dose of amikacin in healthy subjects.

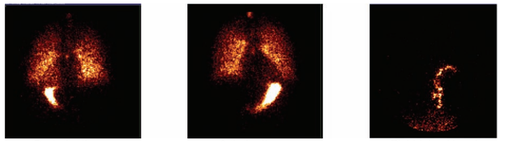

Figure 2: Scintigraphy scan after inhalation of radio-labeled amikacin using PDDS Clinical handheld device in one representative healthy subject.

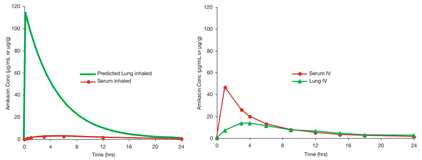

Figure 3: Amikacin concentration versus time in lung (green) and serum (red) after administration of inhaled (left) or IV (right) 400 mg dose.

Parameter	Treatment 1 Inhaled Dose n=13	Treatment 2 Intravenous Dose n=14
Serum C_{max} (µg/mL)	2.8 ± 0.64	32.0 ± 5.3
Serum T_{max} (hours)	3.00 (1.00, 6.00)	0.50 (0.47, 0.55)
Serum AUC (µg/mL•hour)	20.2 ± 5.6	94.8 ± 22.4
Serum $t_{1/2}$ (hours)	3.8 ± 0.9 (N=10)	2.8 ± 0.7
Amount excreted in urine (mg)	80.3 ± 39.1	372.1 ± 118.0

Table 2: Pharmacokinetic results in healthy subjects after aerosolized amikacin and after IV amikacin.

MVP with Gram-negative Pneumonia

- The C_{max} in TA and in serum on Day 3 in patients treated with the dosing regimen 400 mg q12h as well as the C_{max} in bronchial secretions and serum as described in the literature[3] are reported in Table 3.
- As previously reported, the mean number of IV AB at the end of aerosol treatment (mean 7 days) was 2 times greater with placebo than with q12h aerosolized amikacin ($p<0.02$).[4]
- Of 76 reported treatment-emergent adverse events (AEs), 2 (both bronchospasm) were considered probably related to amikacin. There were a total of 25 serious AEs reported by 20 patients. None was related to amikacin treatment. There were no serious AEs considered related to the PDDS Clinical.

Parameter	Aerosolized amikacin 400 mg q12 h on Day 3* (n=21)	IV amikacin 15 mg/kg/day administered once-daily on Day 1** (n=5)[3]
Tracheal Aspirate* or Bronchial Secretion** C_{max}	16,212 ± 3,675 µg/mL†	14.0 ± 4.2 µg/mL
Serum C_{max}	3.2 ± 0.5 µg/mL‡	47 ± 4.2 µg/mL

Table 3: Pharmacokinetic results in MVP on Day 3 after administration of aerosolized amikacin and results from historical controls on Day 1 after administration of IV amikacin 7.5 mg/kg q12h.
†n=14, ‡n=21

Conclusions

Healthy Volunteers

- On average, 43% of the 400 mg inhaled amikacin dose was delivered to the lungs by the PDDS Clinical handheld device. Under normal conditions of ventilation, standard pneumatic nebulizers deliver less than 10% of the nominal dose to the patient's lungs.[7,8]
- Aerosolized amikacin is deposited consistently in the lung after inhalation.
- Low levels of systemic exposure are achieved with the PDDS Clinical as compared to IV administration.
- Inhalation of amikacin solution resulted in a lower serum C_{max} and AUC, and a prolonged T_{max} and $t_{1/2}$ of amikacin as compared with IV infusion.
- The percentage of amikacin excreted in the urine was lower for the inhaled administration (45.9%) of amikacin solution than the IV infusion (85.5%), consistent with the observed lower absolute bioavailability (approximately 60%).
- No serious adverse events were reported and the study medication was generally well tolerated by all healthy subjects.

MVP Patients

- On average, tracheal aspirate concentrations after aerosolized amikacin were 5,000 times higher than that in serum. These high concentrations were approximately 1,100 times higher than that following IV administration.
- Aerosolized amikacin administered q12h is associated with a reduction in the amount of concomitant IV AB required to treat MVP with Gram-negative pneumonia.
- Of the 25 serious AEs, none were related to amikacin treatment or the PDDS Clinical.

Overall Conclusions

- Low serum concentrations of amikacin are detected in healthy subjects and intubated patients with pneumonia after administration of NKTR-061 (inhaled amikacin).
- The use of NKTR-061 administered as 400 mg q12h using the PDDS Clinical achieves greater lung exposure with lower overall doses of amikacin, while reducing serum exposure and concomitant IV AB therapy. Such effects may lead to increased efficacy, reduced incidence of AB resistance, and decreased AB toxicity when used adjunctively in MVP with Gram-negative pneumonia. Further evaluation in a large Phase III clinical study is recommended.

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