NKTR-061 (Inhaled Amikacin) BID Achieves High Epithelial Lining Fluid Concentrations in Pneumonic Portions of Lung

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Abstract

Introduction: The use of systemic aminoglycosides to treat ventilated patients with Gram-negative pneumonia (GNP) is limited by toxicity and poor penetration into the lung.[1] Aerosolization of these drugs may achieve better diffusion in the alveolar compartment. **Objective:** This study was conducted to evaluate NKTR-061 penetration into the epithelial lining fluid (ELF) of the lower respiratory tract of the infected lung in patients with pneumonia. **Methods:** NKTR-061 was administered for 7-14 days via the pulmonary drug delivery system (PDDS Clinical, Nektar Therapeutics) to mechanically-ventilated patients with GNP. The aerosol therapy was an adjunct to IV therapy in accordance with ATS guidelines.[2] Twenty-eight evaluable patients received amikacin (AMK) 400 mg q12h. On day 3 of treatment, patients underwent bronchoalveolar lavage (BAL) 30 minutes after the administration of NKTR-061 aerosol. The ELF was obtained from the infected area of the lung. The apparent volume of ELF recovered by BAL was determined by using urea as an endogenous marker of dilution. On the same day, AMK concentration was determined in serum collected 0.5, 1, 3, 6, 9, 12, 13, and 24 hours after delivery of the morning dose. **Results:** Median (range) ELF AMK concentration was 976.1 µg/mL (135.7-16,127.6), always exceeding the AMK minimum inhibitory concentration (MIC) for microorganisms usually responsible for GNP. Median (range) serum C_{max} was 0.9 µg/mL (0.62- 1.73). Median (range) duration of aerosol treatment was 7 days (2-10). **Conclusions:** Delivery of aerosolized AMK using the PDDS Clinical achieved very high aminoglycoside concentrations in the ELF, including in pneumonic area of the lung, while maintaining safe serum AMK concentrations. The ELF concentrations achieved always exceeded the AMK minimum inhibitory concentration (MIC) for microorganisms usually responsible for GNP. The clinical impact of this route of medication delivery remains to be determined.

Introduction

- The incidence of nosocomial pneumonia ranges from 5 to 10 cases per 1000 hospital admissions in patients without major risk factors, but increases 6- to 20- fold in intensive care unit (ICU) patients who are receiving mechanical ventilation.[2]
- Gram-negative pneumonia (GNP), commonly observed in ventilator- and hospital-associated pneumonia (VAP and HAP, respectively) is a severe respiratory infection with an associated mortality in the range of 25% to 50% despite broad-spectrum antibiotic therapy.[3]
- Amikacin is an aminoglycoside antibiotic with a spectrum of activity suitable for the treatment of nosocomial pneumonia, where Gram-negative organisms are major pathogens.[4]
- Parenteral delivery of aminoglycosides such as amikacin can cause significant adverse systemic side effects (neurotoxicity, nephrotoxicity, and ototoxicity) and results in poor penetration of drug into respiratory secretions.[2]
- The use of aerosolized antibiotics, such as amikacin, as adjuncts to IV antibiotic therapy of ventilated patients with deep lung infections has been hampered by the low efficiency of pulmonary drug delivery when using conventional nebulizers connected to ventilator circuits.[5]
- The proprietary Pulmonary Drug Delivery System (PDDS Clinical) is a novel device that can deliver 50% to 75% of the nominal amikacin dose to the lungs, whereas standard nebulizers deliver less than 10% of the nominal dose to the patient's lungs.[6,7]

Objectives

- To determine the pharmacokinetic profile of aerosolized amikacin administered via the PDDS Clinical, as shown in figure 1, in patients with nosocomial pneumonia caused by Gram-negative organisms.
- To measure the concentration of amikacin in the epithelial lining fluid after aerosolized amikacin administered via PDDS Clinical in intubated and mechanically ventilated patients with nosocomial pneumonia caused by Gram-negative organisms.
- To evaluate the safety and tolerability of aerosolized amikacin administered via PDDS Clinical in patients with nosocomial pneumonia caused by Gram-negative organisms.

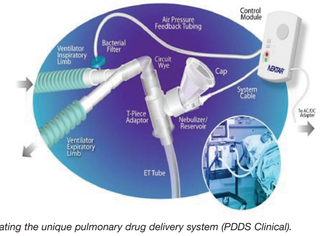

Figure 1: Diagram illustrating the unique pulmonary drug delivery system (PDDS Clinical).

Materials and Methods

Screening/Baseline	Treatment Period	Follow-Up Period
Mechanically ventilated patients Nosocomial pneumonia caused by Gram-negative bacteria Expected to remain intubated for at least 3 days	Amikacin inhalation 400 mg q12h via PDDS Clinical x 7-14 days as adjunct to IV antibiotics PK Assessments Day 3 • Mean C_{max}, time to C_{max} (T_{max}), and AUC • Concentration of amikacin in BAL/ELF samples Safety Assessments • Exposure to study medication, serum creatinine, AE, vital signs, chest X-rays, and weaning	Follow-Up Visit – Day 28 after first dose • Physical exam • Vital signs • Chest X-ray • Hematology • Serum chemistry • Urinalysis • Concomitant medication • Adverse events

Figure 2: Study design and study endpoints.

Key Inclusion/Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
18 years or older	Primary lung cancer or another malignancy metastatic to the lungs
Intubated and mechanically ventilated	Tuberculosis, cystic fibrosis, AIDS or *Pneumocystis carinii* pneumonia
Diagnosis of pneumonia • New or progressive infiltrates on chest X-ray • Presence of Gram-negative organisms (Gram stain or BAL/TA) • Remain intubated and mechanically ventilated for at least 3 days • Plus 2 of the following: • Fever (oral >38.0°C (100.4°F); rectal >38.5°C (101.3°F); or hypothermia, rectal <35.0°C (95.2°F)) • Leucocyte count ≥10,000/mm³ or ≤4,500/mm³ • New onset of purulent sputum production or respiratory secretions, or a change in the character of sputum	• Receiving chronic immunosuppressive therapy • BMI > 33 kg/m² • Chronic liver disease • End-stage renal disease or dialysis • Serum Creatinine > 2mg/dL at screening

Results

Study Population

- 30 patients were enrolled in the study to receive 400 mg of aerosolized amikacin twice daily using PDDS Clinical.
- All 30 patients enrolled were included in the safety population.
- Twenty-eight patients were included in the PK population.†

† The pharmacokinetic population was defined as all treated patients who had any evaluable pharmacokinetic data for any of the four specimen types (serum, urine, tracheal aspirates, and in BAL/ELF) at Day 3 and had received at least 3 full days of study medication.

Baseline Demographics

Baseline Demographic	Amikacin 400 mg every 12 hours (n=30)
Age (years) Mean (SD) Median (Min, Max)	 46.8 (16.13) 49.0 (19, 76)
Sex, n (%) Male Female	 23 (76.7%) 7 (23.3%)
Race, n (%) Caucasian Black Hispanic	 22 (73.3%) 5 (16.7%) 3 (10.0%)
Body Mass Index (kg/m²) (n=29) Mean (SD) Median (Min, Max)	 27.41 (3.659) 27.20 (20.7, 37.9)

Table 2: Baseline demographics.

Pharmacokinetic Results

Serum Analyses

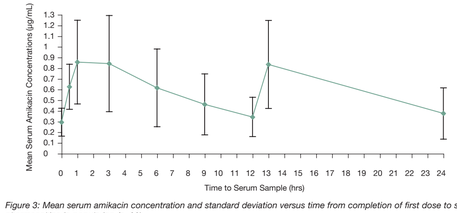

Figure 3: Mean serum amikacin concentration and standard deviation versus time from completion of first dose to serum sample on day 3: pharmacokinetic population (n=28).

- One hour after dosing on Day 3, the mean peak (C_{max}) was 0.95 µg/mL with a standard deviation (SD) of 0.43 (Figure 3).
- The total serum exposures to amikacin during the 12 hours after dosing ($AUC_{0\text{-}12\ hrs}$) (SD) was 6.94 µg·hr/mL (3.75).
- The mean T_{max} (SD) was 1.71 hour (1.30) and the median was 1.00 hour with a range of 0.50 to 5.98.

Site-of-Infection Analyses

Bronchoalveolar Lavage (BAL)/Epithelial Lining Fluid (ELF)	Amikacin 400 mg every 12 hours (n=28)
Median µg/mL (Min, Max)	976.07 (135.67, 16,127.56)
Mean µg/mL (Standard Error)	2,417.57 (688.75)
Standard Deviation	3,644.50
% Coefficient of Variation	150.75
Tracheal Aspirate	**Amikacin 400 mg every 12 hours (n=28)**
Median µg/mL (Min, Max)	1,188.0 (100, 10,480)
Mean µg/mL (Standard Error)	1,779.8 (257.45)
Standard Deviation	2,138.51
% Coefficient of Variation	120.2

Table 3: Bronchoalveolar lavage/epithelial lining fluid concentration of amikacin 15 to 30 min after dosing on Day 3 and mean tracheal aspirate concentration of amikacin throughout the day on Day 3.

- Fifteen to 30 minutes after dosing on day 3 the mean and median concentrations of AMK in the BAL/ELF were 2,417.57 µg/mL and 976.07 µg/mL, respectively, with a range of 135.67 to 16,127.56 µg/mL.
- The mean and median concentrations of AMK in the first tracheal aspirate samples after dosing were 1,779.8 µg/mL and 1,188.0 µg/mL, respectively, with a range of 100 to 10,480 µg/mL.

Safety Results

Extent of Amikacin Exposure

- Patients were exposed to study drug for a mean duration of 6.3 days and a median (range) of 7 days (2-10).

Serum Creatinine Levels

- Fluctuations in mean serum creatinine concentrations were minimal over the course of the study (Figure 4).

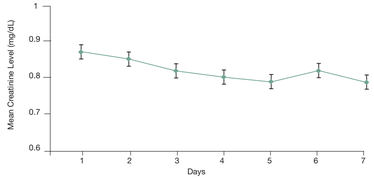

Figure 4: Mean (±SEM) serum creatinine levels versus time for all treated patients Days 1-7. Days 8 (n=3), 9 (n=2), and 10 (n=1) were excluded due to sample size.

Adverse Events

- Eight patients out of 30 experienced 10 serious adverse events (SAE); 5 of these lead to patient death. Only 1 SAE, worsening acute renal failure, was considered possibly related to the study medication. All other SAEs were considered not-related to the study medication or study device.
- There was a total of 355 adverse events (AEs), most were expected and independent of study medication. A total of 64 unexpected adverse events (AEs) were reported for 24 patients; 6 patients had no reports of AEs. The most commonly reported unexpected AEs (n=30) were depression (13.3%), deep vein thrombosis (10.0%), and hypertension (10.0%).
- Three AEs (bronchospasm, acute renal failure, and increased serum creatinine), occurring in two patients, were considered possibly related to the study medication.
- There were no AEs reported related to the study device.

Conclusions

- Delivery of aerosolized AMK using PDDS Clinical achieved very high amikacin concentrations in the tracheal aspirate and the ELF (i.e., the site of infection), while maintaining safe serum amikacin concentrations.
- The reported ELF and tracheal aspirate concentrations always exceeded the amikacin PK and safety MIC for microorganisms usually responsible for GNP.
- These results make aerosolized AMK administered via the PDDS Clinical a highly viable option for primary adjunctive therapy in Gram-negative pneumonia. Phase III clinical studies conducted on a larger scale may further validate these findings.

References

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