

Pharmacokinetics of novel anti-Gram-negative antibiotics in rats

Feda' E.A. Ali,¹ Guoying Cao,¹ Anima Poudyal,¹ Timo Vaara,² Roger L. Nation,¹ Martti Vaara,² Jian Li¹

¹Facility for Anti-infective Drug Development and Innovation, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia

²Northern Antibiotics Ltd., Helsinki, Finland

ABSTRACT

Background: Gram-negative pathogens resistant to all available antibiotics are presenting a global medical challenge. This study examined the pharmacokinetics (PK) of 3 novel polymyxin-like anti-G- compounds (chemical structures in the U.S. Patent Application 11/891,629) in rats. **Methods:** NAB 739, 741 or 7061 (1 mg/kg) was administered to male Sprague-Dawley rats as an intravenous bolus. Blood samples were collected before dosing and at 10, 20 and 30 min, 1, 1.5, 2, 3 and 4 h after administration. To determine the urinary recovery of unchanged drug, urine samples were collected in 0 – 4 h, 4 – 6 h and 6 – 24 h intervals. Plasma and urine samples were stored at -80°C until analysed using HPLC (NAB 7061) or liquid chromatography/mass spectrometry (NAB 739 & 741). Non-compartmental analysis of the plasma PK of the compounds was performed. **Results:** All 3 compounds were well tolerated. PK parameters for them are shown in Table; colistin data after IV administration (1 mg/kg) in rats (AAC 2003, 47: 1766) are included for comparative purposes. NAB 739 and 7061 had similar half-lives as colistin. All NAB compounds had much higher urinary recovery than observed for colistin. Thus, while the total body clearances of the NAB compounds and colistin were within ~3-fold range, renal clearance was a greater contributor for the NAB compounds than for colistin. **Conclusions:** This is the first PK study of these novel anti-Gram-negative antibiotics in animals. Minor alterations in the chemical structures appear to have important impacts on their PK including changing the relative contributions of renal and non-renal clearances to the total clearance.

INTRODUCTION

- Infections caused by extreme drug-resistant Gram-negative enteric bacteria, such as *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have presented a global medical challenge and highlighted the unmet medical need for new antibiotics.¹
- Although polymyxins have been used as a last-line therapy against these difficult-to-treat pathogens, unfortunately, resistance to polymyxins has been increasingly reported recently.²
- There is an urgent need to develop novel antibiotics against these extreme drug-resistant pathogens.¹
- Very recently novel polymyxin-like antibiotics have been developed (U.S. Patent Application 11/891,629) which possess similar antibacterial activity but better toxicity profiles than polymyxins.³

AIM

- To examine the pharmacokinetics (PK) of three novel polymyxin-like anti-Gram-negative compounds in rats.

METHODS

- NAB 739, 741 or 7061 (1 mg/kg) was administered to male Sprague-Dawley rats as an intravenous (IV) bolus.
- Blood samples were collected before dosing and at 10, 20 and 30 min, 1, 1.5, 2, 3 and 4 h after administration.
- Urine samples were collected in 0 – 4 h, 4 – 6 h and 6 – 24 h intervals to determine the urinary recovery of unchanged drug.

- Plasma and urine samples were stored at -80°C until analysed using HPLC (NAB 7061) or liquid chromatography/mass spectrometry (NAB 739 and 741).
- Non-compartmental analysis of the plasma PK of the compounds was performed.

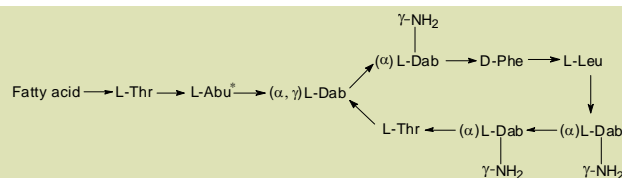


Figure 1: Chemical structures of NAB 739 and NAB 7061. Fatty acid = octanoic acid, Thr: threonine; Abu: α -Aminobutyric acid; Dab: α,γ -Diaminobutyric acid; Phe: phenylalanine; Leu: leucine. In NAB 739, D-Ser (serine) replaces the L-Abu marked with the asterisk. α and γ indicate the respective amine group involved in the peptide linkage.

RESULTS

- NAB 739, 741 or 7061 (Figure 1) were well tolerated in rats.
- Figure 2 shows plasma concentration - time profiles for NAB 739, 741 and 7061 in rats following an intravenous dose (1 mg/kg).
- The mean extrapolated AUC represented $7.87 \pm 5.84\%$, $0.82 \pm 0.50\%$ and $7.43 \pm 3.11\%$ of total AUC of NAB 739, 741 and 7061, respectively.
- PK parameters for all NAB compounds are shown in the Table; colistin data in rats⁴ are included for comparative purposes.
- All NAB compounds had much higher urinary recovery than observed for colistin (Table).

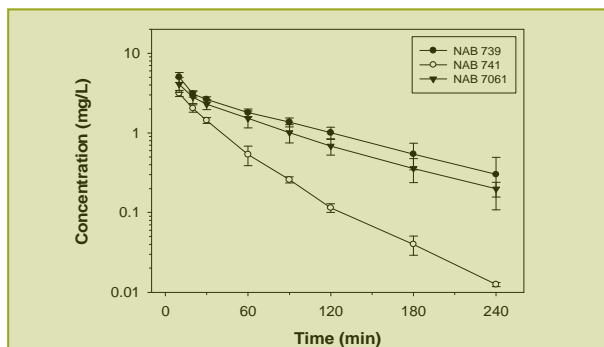


Figure 2: Plasma concentration (mean \pm SD) vs time profiles for NAB 739 (n = 4), 741 (n = 4) and 7061 (n = 5) in rats following an IV dose (1 mg/kg).

Table: Pharmacokinetic parameters for NAB 739, 741, 7061 and colistin⁴ following IV administration in rats (mean \pm SD)

PARAMETER	NAB 739	NAB 741	NAB 7061	COLISTIN
Half-life (min)	69.0 \pm 21.9	32.7 \pm 2.41	66.2 \pm 12.3	74.6 \pm 13.2
Volume of distribution (mL/kg)	222 \pm 20.5	243 \pm 24.0	339 \pm 96	496 \pm 60
Clearance (mL/min/kg)	2.63 \pm 0.54	7.39 \pm 0.85	3.84 \pm 0.75	5.22 \pm 0.41
Urinary recovery (% of dose)	19.4 \pm 7.38	50.9 \pm 13.6	7.16 \pm 3.70	0.18 \pm 0.14
Renal clearance (mL/min/kg)	0.53 \pm 0.30	3.78 \pm 1.11	0.28 \pm 0.16	0.010 \pm 0.008

DISCUSSION

- Similar to colistin, NAB 739 and 7061 were predominantly non-renal cleared; renal (CL_R) and non-renal clearance (CL_{NR}) contributed approximately equally to the total clearance of NAB 741.
- Substantially different CL_R of NAB 739, 741 and 7061 indicate differences in their renal handling. Renal clearance was a greater contributor to respective total clearance for the NAB compounds than for colistin.
- Comparison of CL_{NR} of NAB 739, 741 and 7061 with normal hepatic blood flow in the rat (72 – 95 mL/min/kg) indicates that all NAB compounds must have a very low hepatic extraction ratio, similar to colistin⁴.
- The presence of a hydroxyl group in the D-serine of NAB 739 leads to a lower CL , which is due to a lower CL_{NR} compared to that for NAB 7061.
- It appears that the presence of positively charged Dab residues in the peptide side chain play an important role in the renal elimination of polymyxins and these polymyxin-like NAB compounds, and possibly in nephrotoxicity³.

CONCLUSION

- It is evident that the differences in the chemical structures across NAB compounds and colistin led to differences in their pharmacokinetics.
- There are substantial differences in relation to renal handling and the relative contributions of CL_R and CL_{NR} to overall elimination from the body among NAB compounds and colistin.

REFERENCES

- Talbot GH, Bradley J, Edwards JE, Jr, et al. Clin Infect Dis 2006; 42:657-668.
- Li J, Nation RL, Turnidge JD, et al. Lancet Infect Dis 2006; 6:589-601.
- Vaara M, Fox J, Loidl G, et al. Antimicrob Agents Chemother 2008; 52:3229-3236.
- Li J, Milne RW, Nation RL, et al. Antimicrob Agents Chemother 2003; 47:1766-1770.

ACKNOWLEDGMENT

This project was supported by Northern Antibiotics Ltd., Helsinki, Finland.