



Novel Polymyxin Derivatives Effective in Treating Experimental Peritoneal *E. coli* Infection in Mice

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BACKGROUND

Gram-negative bacteria are progressively becoming more resistant to the clinically available antibacterial agents. This has reinstated polymyxins as the drugs of last resort to treat serious infections caused by multi drug resistant gram-negatives. In the present investigation we evaluated the *in vivo* efficacy of three novel polymyxin derivatives against the common opportunistic pathogen *E. coli* in a murine peritoneal infection model.

MATERIALS AND METHODS

Mice were inoculated intraperitoneally with 10⁶ CFU of the virulent *E. coli* strain IH3080 (O18:K1). At 1 and 3 hrs post infection mice (n=3-4) were treated with the polymyxin derivatives NAB737, NAB739 and NAB7061. Control mice received saline. The clinical status of the mice and bacterial load in the peritoneum were determined at the time of treatment and at 1 or 4 hrs after the last treatment.

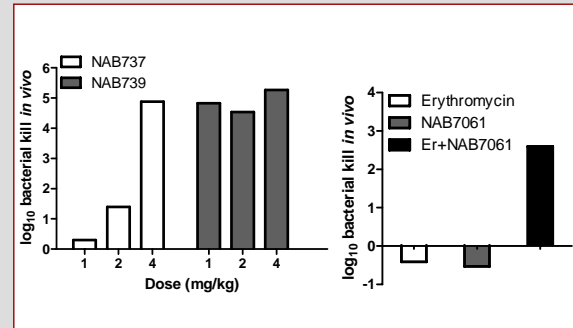
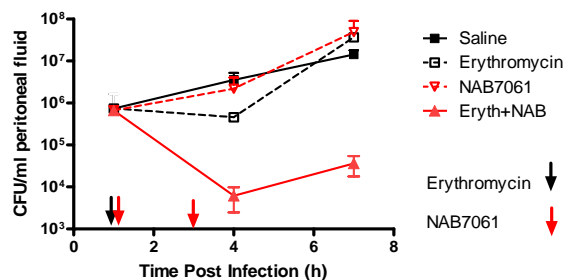
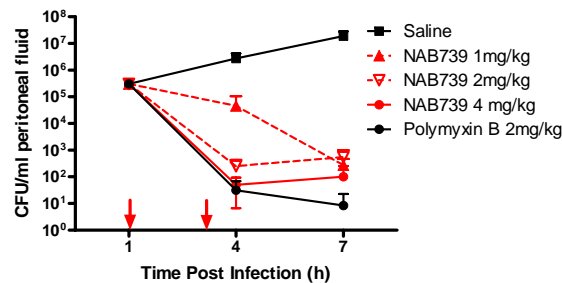
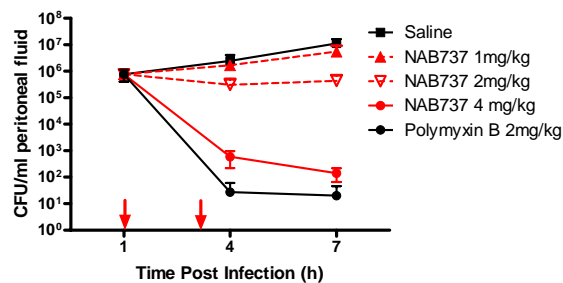
The structure of polymyxin B and three NAB compounds.

Polymyxin B	MHA/MOA	Dab-Thr-Dab-	cy[Dab-Dab- <i>o</i> Phe-Leu-Dab-Dab-Thr]
NAB7061	OA-	Thr- Abu-	cy[Dab-Dab- <i>o</i> Phe-Leu-Dab-Dab-Thr]
NAB737	OA-	Thr- <i>o</i> Thr-	cy[Dab-Dab- <i>o</i> Phe-Thr- Dab-Dab-Thr]
NAB739	OA-	Thr- <i>o</i> Ser-	cy[Dab-Dab- <i>o</i> Phe-Leu-Dab-Dab-Thr]

Abbreviations:

MHA/MOA, the mixture of 6-methylheptanoic acyl and 6-methyl octanoic acyl; **OA**, octanoic acyl; **Dab**, diaminobutyric acid residue; **Abu**, aminobutyric acid residue; **cy**, cyclo. The residues marked with red denote those that carry a free amino group.

Treatment of Experimental Peritonitis



RESULTS

- Treatment with NAB737 at 4 mg/kg resulted in a 4.9 log₁₀ bacterial kill *in vivo*.
- Treatment with NAB739 at 4 mg/kg resulted in a 5.3 log₁₀ protection and at 1 mg/kg a 4.8 log₁₀ bacterial kill *in vivo*
- Treatment with NAB7061 at 5 mg/kg in combination with erythromycin (20mg/kg) resulted in a 2.9 log₁₀ bacterial kill *in vivo*.

CONCLUSION

We found that the novel polymyxin derivatives NAB737, NAB739 and NAB7061 have potent *in vivo* bactericidal effect against *E. coli* in an experimental murine peritonitis model.

REFERENCE

Vaara M. et al. Novel polymyxin derivatives carrying only three positive charges are effective antibacterial agents. Antimicrob Agents Chemother. 2008;52(9):3229-36.