A042

Pharmacodynamics of Amikacin Against Aerobic Gram-Negative Rods Studied in an In Vitro Model of Infection

KE Bowker, AR Noel, D Nicholls, SG Tomaselli, AP MacGOWAN

BCARE, Department of Microbiology, North Bristol NHS Trust, Bristol, UK

karen.bowker@nbt.nhs.uk

54th ICAAC, Washington Sept 5-9th 2014

Amended Abstract

Background:
Initial pre-clinical studies of aminoglycoside pharmacodynamics were performed twenty-five years ago, using a limited number of strains and not employing modern analytical methods. Inhalational aminoglycosides are increasingly popular as adjunct therapy for HAP, VAP and HCAP and, as such, meet the requirements of modern pharmacodynamic principles – that is, high exposure, short duration, combination therapy. We used an in vitro dilutional pharmacokinetic model to simulate a range of amikacin exposures based on pK in respiratory tract secretions in order to establish the fAUC/MIC for bacteriostatic and bactericidal effects against aerobic Gram-negative respiratory pathogens.

Methods:
Six strains of Gram-negative rods were employed – 3 strains *K.pneumoniae* (MIC 1.5, 3.0mg/L); 3 strains *P.aeruginosa* (MIC 2.0mg/L, 32mg/L). A dilutional single compartment model was used to simulate free drug exposures based on amikacin pK in ELF following inhalation (t½ 1.1hr). Antibacterial effect was measured over 48hrs by changes in log CFU/ml. fAUC/MIC from 0-210 were modelled for each strain. Log changes in viable count (log CFU/ml) were related to fAUC/MIC using an Emax model.

Results:
The measured amikacin concentrations were as expected. The fAUC/MIC for 24hrs static, -1, -2 log drop were 37 ± 18, 58 ± 20 and 86 ± 32 respectively. Equivalent values after 12hrs were 19 ± 16, 34± 30, 69 ± 60. The fAUC/MIC for antimicrobial effect at 48hrs were similar to those at 24hrs and MIC had no effect on the exposure response relationship.

Conclusions:
Previous data based on single strains of *P.aeruginosa* or *E.coli* indicated an AUC/MIC in the range 50-70 was associated with a 24hr bacteriostatic effect and an AUC/MIC of 120-130 with -2 log drop. Our data indicates these estimates may be conservative as our AUC/MIC sizes are on the lower end of these ranges. In addition the data highlights the rapid early kill obtained with amikacin as evidenced by the lower AUC/MIC targets at 12hrs compared to 24 and 48hrs and suggests that strains with high MICs behave in a similar way to those with low MIC values.

Introduction

- Pulmonary infection accounts for 65% of all ICU infection, and around 15–20% of patients have ventilator associated pneumonia (VAP). Mortality (approx 25–50%) is associated with more complications, longer ICU stay and increased healthcare costs.
- Due to the scarcity of antimicrobial agents for Gram-negative infections in development pipelines, novel approaches are required to 1) optimise therapeutic outcomes using existing drug classes, and 2) suppress emergence of resistance to currently available agents.
- Inhalational antibiotics produce very high lung concentrations, reducing associated risks of emergence of resistance and, for aminoglycosides, reduced systemic toxicity.
- Amikacin Inhale is being developed by Bayer HealthCare and Nektar Therapeutics for adjunctive treatment of intubated, mechanically ventilated patients with Gram-negative pneumonia. Amikacin Inhale is currently being evaluated in Phase III trials. It consists of a specially formulated amikacin solution (400mg, 3.2 mL of 125 mg/mL, q12 hours for 10 days) aerosolized using the Pulmonary Drug Delivery System (PDDS) - a disposable, proprietary vibrating mesh nebulizer.
- Phase II clinical studies in ventilated patients receiving Amikacin Inhale 400mg 12hrly have shown tracheal aspirate at peak concentration 16,200mg/L ± 3,700, elimination half-life was around 1–2 hours.
- Patients receiving 400mg 12 hrly Amikacin Inhale had mean 15–30 minutes lung epithelial lining fluid (ELF) concentration after starting administration of 2,417mg/L.
- The pD of systemic aminoglycosides for Gram-negative bacteria is AUC/MIC or Cmax/MIC. A peak/MIC ratio of 8–10 has been shown in pre-clinical models to decrease the risk of EoR and has been linked to optimised clinical outcome in man.
- The MIC distributions of potential target pathogens indicate the vast majority of aerobic Gram-negative rods have MIC values of ≤64mg/L (www.eucast.org, accessed August 2014).

Aim of Study

To simulate a range of amikacin exposures to establish the fAUC/MIC and fCmax/MIC for bacteriostatic and bactericidal effects against Gram negative respiratory pathogens.

Materials and methods

- 3 strains each of *P.aeruginosa* and *K. pneumoniae* with amikacin MICs 1.5–64mg/L were utilised.
- A dilutional single compartment IVPKM using Mueller Hinton broth was used to simulate free drug concentrations of AMI; Cmax/MIC 0–60mg/L; AUC/MIC 0–501mg/l.h, half-life 1.1h.
- Antibacterial effect (ABE) was measured over 48h by log changes in CFU/ml. ABE was related to Cmax/MIC and AUC/MIC using an Emax model.

Results

- Tables 1 and 2 show the MIC and the individual and mean fCmax/MIC and fAUC/MIC respectively for each strain at 12, 24 and 48h.
- Figures 1a and b and Figures 2a and b show the relationship between fCmax/MIC and fAUC/MIC with log reduction in viable at 12, 24 and 48h for *K. pneumoniae* and *P. aeruginosa*.
- MIC did not impact on the exposure response relationship.
- The meaned (all strains) static and -1log drop values were similar for both fAUC/MIC i.e. 36.8 ± 18.1 and 37.3 ± 11.7, and 57.7± 19.5 and 70.4 ± 19.0 (respectively) and fCmax/MIC 12.9 ± 7.2 and 13.8 ± 5.7, and 23.2 ± 18.5 and 20.8 ± 6.5 at 24h and 48h (Tables 1 and 2).
- The fCmax/MIC and fAUC/MIC values were lower for *P. aeruginosa* at 12h, 24h and 72 in comparison to *K. pneumoniae* (Tables 1 and 2, Figures 1 and 2).

Table 1: Relationship between fAUC/MIC and log reduction in viable count

12h		fCmax/MIC		
	MIC (mg/L)	static	-1 log drop	-2log drop
K.pneumoniae 41966	1.5	14.9	19.0	35.4
K.pneumoniae 41965	3	6.6	10.5	16.0
K.pneumoniae 49162	64	5.0	8.8	14.8
mean (n=3)		**8.8 ± 5.3**	**12.8 ± 5.5**	**22.1 ± 11.6**
P.aeruginosa 41961	2	1.9	2.5	-
P.aeruginosa 41959	6	13.7	28.6	53.7
P.aeruginosa 41957	32	1.0	2.2	4.0
mean (n=3)		**5.5 ± 7.1**	**18.6 ± 14.3**	**26.9**
mean (all strains n=6*)		**7.2 ± 5.9**	**11.2 ± 10.2**	**24.8 ± 17.9**
24h		**fCmax/MIC**		
	MIC (mg/L)	static	-1 log drop	-2log drop
K.pneumoniae 41966	1.5	15.0	23.3	-
K.pneumoniae 41965	3	14.0	20.7	27.7
K.pneumoniae 49162	64	9.9	13.4	19.3
mean (n=3)		**14.2**	**19.6**	**26.1**
P.aeruginosa 41961	2	7.7	15.5	27.8
P.aeruginosa 41959	6	25.6	59.0	-
P.aeruginosa 41957	32	5.4	7.0	9.6
mean (n=3)		**12.9 ± 11.1**	**27.2 ± 27.9**	**18.7**
mean (all strains n=6*)		**12.9 ± 7.2**	**23.2 ± 18.4**	**21.1 ± 18.6**
48h		**fCmax/MIC**		
	MIC (mg/L)	static	-1 log drop	-2log drop
K.pneumoniae 41966	1.5	22.4	30.4	37.7
K.pneumoniae 41965	3	16.6	22.9	31.4
K.pneumoniae 49162	64	8.0	14.3	18.4
mean (n=3)		**15.7 ± 7.2**	**22.5 ± 8.1**	**29.2 ± 9.8**
P.aeruginosa 41961	2	10.9	21.1	41.5
P.aeruginosa 41959	6	-	-	-
P.aeruginosa 41957	32	11.2	15.4	20.5
mean (n=3)		**11.1**	**18.3**	**31.0**
mean (all strains n=5)		**12.9 ± 7.2**	**23.2 ± 18.4**	**21.1 ± 18.6**

Figure 1:Relationship between fCmax/MIC and log reduction in viable count

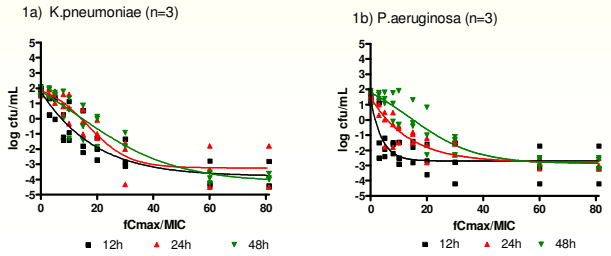
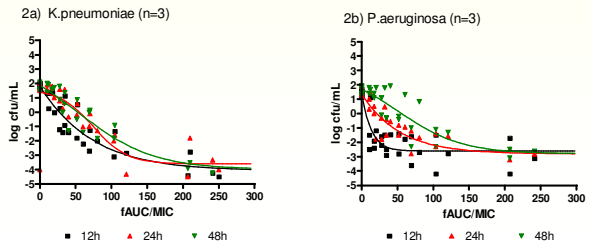


Table 2: Relationship between fAUC/MIC and log reduction in viable count

12h		fAUC/MIC		
	MIC (mg/L)	static	-1 log drop	-2log drop
K.pneumoniae 41966	1.5	48.3	88.1	169.7
K.pneumoniae 41965	3	22.2	35.4	52.0
K.pneumoniae 49162	64	20.0	37.0	58.6
mean (n=3)		**30.2 ± 15.7**	**53.5 ± 30.0**	**93.4 ± 66.1**
P.aeruginosa 41961	2	6.3	6.9	-
P.aeruginosa 41959	6	12.8	28.6	52.5
P.aeruginosa 41957	32	4.0	7.0	12.8
mean (n=3)		**7.7 ± 4.6**	**14.2 ± 12.5**	**32.7**
mean (all strains n=6*)		**18.9 ± 16.1**	**33.8 ± 29.8**	**69.1 ± 59.1**
24h		**fAUC/MIC**		
	MIC (mg/L)	static	-1 log drop	-2log drop
K.pneumoniae 41966	1.5	66.2	84.2	-
K.pneumoniae 41965	3	49.3	68.1	99.7
K.pneumoniae 49162	64	37.3	57.2	80.0
mean (n=3)		**50.9 ± 14.5**	**69.8 ± 13.6**	**89.9**
P.aeruginosa 41961	2	23.6	56.2	102.8
P.aeruginosa 41959	6	25.0	55.8	113.9
P.aeruginosa 41957	32	19.5	24.7	33.1
mean (n=3)		**22.5**	**43.3**	**85.8**
mean (all strains n=6*)		**36.2 ± 18.1**	**57.7 ± 19.5**	**85.9 ± 31.9**
48h		**fAUC/MIC**		
	MIC (mg/L)	static	-1 log drop	-2log drop
K.pneumoniae 41966	1.5	59.0	102.5	129.7
K.pneumoniae 41965	3	38.9	79.2	107.4
K.pneumoniae 49162	64	35.6	53.1	72.5
mean (n=3)		**44.5 ± 12.7**	**78.3 ± 24.7**	**103.2 ± 28.8**
P.aeruginosa 41961	2	31.0	74.3	147.9
P.aeruginosa 41959	6	24.7	55.8	112.2
P.aeruginosa 41957	32	34.7	57.3	100.0
mean (n=3)		**30.1 ± 5.1**	**62.5 ± 10.3**	**120.0± 24.9**
mean (all strains n=6)		**37.3 ± 11.7**	**70.4 ± 19.1**	**111.6 ± 25.8**

Figure 2: Relationship between fAUC/MIC and log reduction in viable count



Conclusions

- Our data showing AUC/MIC 19.5–25.0 for a 24h static effect and 33.1–113.9 for a -2log kill is lower than that of previous data using single strains of *P. aeruginosa* (50–70, 120–130 respectively).
- Rapid early kill was obtained with AMI as evidenced by the lower AUC/MIC targets at 12hrs compared to 24 and 48hrs.
- These data also demonstrate that strains with high MICs behave in a similar way to those with low MIC values.
- Some species difference was noted between *K. pneumoniae* and *P. aeruginosa*.

Bristol Centre for Antimicrobial Research and Evaluation

North Bristol NHS Trust