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The pharmacodynamics of plazomicin and amikacin studied in an in vitro pharmacokinetic model

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Introduction

- Aminoglycoside antibiotics have been a mainstay of antimicrobial chemotherapy for more than forty years yet the pre-clinical data on their pharmacokinetics-pharmacodynamics (PK-PD) is scarce.
- Published data points to AUC/MIC or Cmax/MIC as the dominant pharmacodynamic index (PDI) with an AUC/MIC of 50-70 being associated with 24h static effect for aerobic Gram-negative rods (*Enterobacteriaceae* and *Pseudomonas aeruginosa*).
- Plazomicin (plazomicin sulphate, previously ACHN-490) is a next-generation aminoglycoside antibiotic that has completed Phase 3 clinical studies including treatment of patients with serious bacterial infection due to multi-drug resistant *Enterobacteriaceae*.
- Plazomicin was designed to evade modification by aminoglycoside modifying enzymes.
- Administration of once-daily 15mg/Kg in man produced a Cmax of 144±45mg/L, total drug AUC of 246±39mg/L.h, a half-life of 3.4±0.8h and a protein binding of 16±5%.

Aims of Study

To define the exposure-effect relationship for plazomicin and a comparator aminoglycoside (amikacin) and the antibacterial effect in an in vitro pharmacokinetic model for Enterobacteriaceae with different resistance mechanisms.

Materials and methods

- An in vitro dilutional single compartment pharmacokinetic model was used.
- Dose ranging experiments were conducted based on a plazomicin half-life 3.4h and an amikacin half-life 2.5h.
- Aminoglycoside PK is best described using tri-phasic elimination, the significance of drug concentrations during the gamma elimination phase on bacterial kill kinetics is unclear and difficult to model. To probe this phenomenon, both drugs were administered 24hrly or 12hrly in different experiments to explore the effects of the gamma phase on bacterial killing.
- The strains of *E.coli* and *K. pneumoniae* used are shown on Table 1.
- Bacterial viable counts were determined at T0-T7, T12, T24, T36 and T48 hrs with an initial inoculum of 10^6CFU/ml.
- Plazomicin concentration was determined by LCMS-MS by Alturas Analytics, Moscow, USA and amikacin by QMS immunoassay.

Results

- Target versus expected plazomicin $R^2$0.92 and amikacin $R^2$0.98 concentrations were in excellent agreement.
- The AUC/MIC targets for individual strains and mean data for *E.coli* (n=5) - plazomicin administered 12hrly are shown on Table 2.
- The AUC/MIC targets for individual strains and mean data for *K.pneumoniae* (n=5) for plazomicin administered 12hrly are shown on Table 3

Results

- The AUC/MIC targets for amikacin administered 12hrly against *E.coli* (n=3) were 12h static effect 16.1±10; -1 log drop 22.8±12.5; -2 log drop 32.4±12.4; -3 log drop 59.3±11.9; 24h static effect 49.5±12.7; -1 log drop 55.7±14.8; -2 log drop 64.1±19.5; -3 log drop 73.3±25.3; 48hr static effect 78.6±35.9; -1 log drop 81.0±36.6; -2 log drop 81.8±37.8; -3 log drop 84.2±38.9.
- The AUC/MIC targets for plazomicin and amikacin against *E.coli* when 24h and 12h administration were compared is shown on Table 4.

Table 1: Plazomicin and amikacin MICs and strain resistance mechanisms

Species	Isolate Code	Resistance mechanism	MICs (mg/L)	
			Plazomicin	Amikacin
E.coli	AEC0 1174	ESBL, OXA-48	0.5	1
E.coli	AEC0 1175	ESBL, NDM	1	2
E.coli	AEC0 1177	ESBL	2	2
E.coli	SMH 64979	None	2	-
E.coli	SMH 64982	None	4	-
K.pneumoniae	AKPN 1169	ESBL, KPC	1	-
K.pneumoniae	AKPN 1170	ESBL, KPC, AAC(6)1b	1	-
K.pneumoniae	AKPN 1171	ESBL	2	-
K.pneumoniae	SMH 41965	None	0.5	
K.pneumoniae	SMH 41966	None	0.5	

Table 2: Individual and mean AUC/MIC data for *E.coli* (n=5) - plazomicin 12hrly dosing

Endpoint	AECO 1174	AECO 1175	AECO 1177	64979	64982	Mean ± SD
12h						
Static	4.4	9.3	15.5	9.7	9.7	9.7 ± 3.9
-1 log drop	10.4	10.3	21.4	13.8	14.6	14.1 ± 4.5
-2 log drop	28.5	11.2	31.6	19.4	22.1	22.6 ± 8.0
-3 log drop	90.8	13	53.7	30.8	30.8	43.8 ± 30.0
24h						
Static	67.3	18.6	33.5	33.1	28.2	36.1 ± 18.4
-1 log drop	75	20.7	37.2	34.5	28.8	39.3 ± 20.9
-2 log drop	79.1	23.9	38.9	35.3	28.8	41.2 ± 21.9
-3 log drop	87.1	27.2	42.7	36.3	30.6	44.8 ± 24.4
48h						
Static	129.7	46.2	38.8	56.2	22.9	58.8 ± 41.5
-1 log drop	131.8	52.5	42.7	57.5	25.6	62.0 ± 40.9
-2 log drop	131.8	55.3	45.2	60.3	26.6	63.8 ± 40.1
-3 log drop	134.9	64.6	51.3	61.4	31.6	68.8 ± 39.2

Table 3: Individual and mean AUC/MIC targets for *K.pneumoniae* for plazomicin administered 12hrly

Endpoint	strain AUC/MIC					
	AKPN 1169	AKPN 1170	AKPN 1171	KP41965	KP41966	Mean ± STD
12h						
Static	15.2	66.1	40.7	37.6	17.2	35.3±20.7
-1 log drop	28.8	77.6	49.6	59.3	23.7	47.8±22.2
-2 log drop	53.7	91.2	60.9	101.9	33	68.1±28.1
-3 log drop	113.5	107.2	82.2	275.4	48.2	125.3 ± 87.8
24h						
Static	18.5	38	27.7	58.2	27.5	34.0 ± 15.2
-1 log drop	33.7	42.7	34.9	95.5	27.3	46.8 ± 27.8
-2 log drop	63.5	48.9	47.1	147.9	29.7	67.5 ± 46.6
-3 log drop	226.5	57.5	65	333.4	39.2	144.3 ± 129.8
48h						
Static	11.5	49.6	65.8	103.5	68.4	59.7 ± 33.4
-1 log drop	25.7	53.1	74.1	167.1	113.5	86.7 ± 55.2
- 2 log drop	59.3	59.3	84.7	251.2	184.1	127.7 ± 86.1
-3 log drop	134.3	67.3	104.2	333.4	278.6	183.6 ± 115.9

Table 4: AUC/MIC targets for *E.coli* with plazomicin or amikacin administered 24hrly compared to 12hrly individual and mean AUC/MIC data for *E.coli* (n=5)

Endpoint	24h AUC/MIC target (mean ± STD) for			
	Plazomicin		Amikacin	
	24hrly	12hrly	24hrly	12hrly
12h				
Static	7.6 ± 2.5	9.7 ± 5.6	17.5 ± 18.3	16.1 ± 10.0
-1 log drop	14.6 ± 3.5	14.0 ± 6.4	26.4 ± 27.6	22.8 ± 12.5
-2 log drop	30.7 ± 9.3	23.8 ± 11.0	41.2 ± 42.0	32.4 ± 12.4
-3 log drop	81.4 ± 34.5	52.5 ± 38.9	68.8 ± 64.6	59.3 ± 11.9
24h				
Static	141.4 ± 77.4	39.8 ± 24.9	96.2 ± 20.8	49.5 ± 12.7
-1 log drop	152.2 ± 88.7	44.3 ± 27.8	104.5 ± 22.8	55.7 ± 14.8
-2 log drop	164.9 ± 105.8	47.3 ± 28.5	111.9 ± 23.2	64.1 ± 19.2
-3 log drop	242.5	52.3 ± 31.1	123.1 ± 31.8	73.3 ± 25.3
48h				
Static	189.1 ± 78.6	71.6 ± 50.5	133.6 ± 52.3	78.6 ± 35.6
-1 log drop	221.7 ± 73.9	75.6 ± 48.9	143.4 ± 59.3	81.0 ± 36.6
-2 log drop	253.1 ± 67.0	77.5 ± 47.4	150.2 ± 68.0	81.8 ± 37.8
-3 log drop	370.9	83.6 ± 44.9	170.9 ± 95.4	84.2 ± 38.9

Conclusions

- Plazomicin AUC/MIC targets for *E.coli* and *K.pneumoniae* for 24h static to -1 log drop were similar to those for amikacin against *E.coli*.
- Plazomicin AUC/MIC targets for -3 log kill tended to be larger for *K.pneumoniae* compared to *E.coli*.
- Administration of either plazomicin or amikacin 24hrly compared to 12hrly noticeably increased the AUC/MIC targets. This is likely an artifact of the difficulty in simulating drug concentrations during the gamma phase of elimination, which is important to suppress regrowth when aminoglycosides are dosed once daily.
- AUC/MIC targets for both aminoglycosides were lower at 12h and greater at 48hr than the 24h values.

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