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Title - Predictive performance of population pharmacokinetic models for amikacin in term neonates

Running heading - Clinical pharmacokinetics of amikacin in neonates

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Supplementary Table I: Demographic details of reported population pharmacokinetic studies for amikacin in neonates

S.no	Model reference	PK Study	No.of Patients	No.of observations	Gestational Age (Weeks)	Post-natal Age (days)	Birth weight (kg)	Body weight (Kg)	Dose (mg/kg)
1	M1	Allegaert et al. a	205	410	28 (24 – 30)	2 (1-3)	1.07 (0.475 – 1.910)	1.05 (0.475 -1.91)	20 q 36 hrs 20 q 24 hrs
2	M2	Allegaert et al. b	715	1862	33 (24 -43)	2 (1-30)	1.99 (0.385 – 4.650)	1.99 (0.384 – 4.780)	15.5 q 24 hrs 17 q 24 hrs 18.5 q 30 hrs 20 q 36 hrs 20 q 42 hrs
3	M3	Botha et al.	53	106	35.1(3.6)	6.3 (3.3)	2.1(0.8)	NA	17.5 fb 15 q 24 hrs 10 fb 7.5 q 12 hrs
4	M4	Cristea et al.	930	2257	32 (24 – 41)	2 (1 – 30)	1.795 (0.38 – 4.77)	1.8 (0.38 – 4.8)	15 q 30 hrs 15 q 36 hrs
5	M5	De Cock et al.	877	2186	33 (24 -43)	2	1.75	1.76	20 q 36 hrs 20 q 24 hrs
6	M6	Guido et al.	27	50	37 (28 -40)	21 (6 -58)	2.6(1.5 – 3.3)	2.65 (1.4 – 4.0)	7.5 q 24 hrs 7.5 q 12 hrs 7.5 q 8 hrs 10 q 12 hrs 10 q 8 hrs
7	M7	Illamola et al._CrCl	202	567	31.8 (24.3 – 41)	28 (1-86)	1.64 (0.45 – 3.89)	1.92 (0.5 – 4.65)	2.8 – 58.4 Q 8 to 48h
8	M8	Illamola et al._PNA	202	567	31.8 (24.3 – 41)	28 (1-86)	1.64 (0.45 – 3.89)	1.92 (0.5 – 4.65)	2.8 – 58.4 Q 8 to 48h
9	M9	Seth K et al.	247	419	35 (25 – 44)	1.23 (0.16 - 21.7)	2.3 (0.9 – 5.2)	NA	15 fb 7.5 q 12h

10	M10	Sherwin et al.	80	358	28 (24-41)	9 (3-64)	0.97 (0.44 – 4.4)	1.03 (0.45 – 4.43)	18 q 48-36 hrs 16 q 36hrs 15 q 24hrs
11	M11	Smits et al.	579	1195	34 (24 -41)	2 (1-30)	2.285 (0.42 – 4.85)	2.1 (0.42 – 5.04)	16 q 48hrs – 17 q 20 hrs
12	M12	Wang et al.	42	142	38 ± 4	10 ± 7	NA	2.9 ± 0.9	7.5 – 10

- Demographic details were given as Median(range) or Mean ± standard deviation
- A total of 12 population pharmacokinetic models were extracted from 11 studies. Illamola et al reported two models, one using CrCl and the other using PNA as acovariate on amikacin cl

Supplementary Table II: Structural model and parameter details of population pharmacokinetic models of amikacin in neonates

Study ID	Structural Model	Variability
M1	CL = 1.49 * (WT/70)^0.75 * (1+SLPCL*(PMA-40)) * RF * Fventilation * VENT * Finotrope * INO * Fiugr * SGA * exp(η[1]) V = 31.7 * (WT/70) * (1+SLPV*PNA) * Finotrope * INO * Fventilation * VENT * exp(η[2]) where Fventilation (on CL) = 0.977, Fventilation (on V) = 1.08 Finotrope (on CL) = 0.945, Finotrope (on V) = 1.09 SLPCL = 0.032, SLPV = 0.005 Fiugr (on CL) = 0.872; SLP is change in parameter respected to variable	Cl = 33.6% V = 45.1%
M2	CL = 0.486 * (WT/70)^.75 * exp(SLPCL * (PCA-24) * FNSAID) * exp(η[1]) V = 40.2 * (WT/70) * exp(η[2]) where SLPCL=0.11, FNSAID=0.788	
M3	CL = 0.031 * BWT^1.45 * P * exp(η[1]) V = 0.316 * WT^1.44 * exp(η[2]) where P = 1.28 for girls and 1.0 for boys	Cl = 18% V = 13% Proportional error – 29%
M4	CL = 0.0495 * (BWT/1.750)^1.34 * (1+PNA/2)*0.22 * Θ(ibuprofen) * Θ(HT) * exp(η[1]) Vc = 0.832 * (CWT/1.750)^0.926 Vp = Vc Q = 0.45 * CL where Θ(Ibuprofen) = 0.838, Θ(HT) = 0.594, HT = Hypothermic treatment	Cl = 30% Additive error – 0.3 mg/L Proportional error – 0.06%
M5	CL = 0.0493 * (BWT/1.750)^1.34 * (1+0.213*(PNA/2) * 0.838^(Ibuprofen) * exp(η[1]) Vc = 0.833 * (CWT/1.760)^0.919 Q = 0.415 * CL Vp = Vc	Cl = 29.8% Residual Proportional error = 6.14% Additive error = 0.267
M6	Ke = 0.232 * (SCR)^(-0.85) * exp(η[1]) V =497 * CWT * exp(η[2])	NA
M7	CL = 0.093 * (CWT/1.92)^0.799 * (CrCl/32.28)^0.659 * exp(η[1]) Vc = 0.641 * (CWT/1.92)^1.04 * exp(η[2]) Vp = 0.478 Q = 0.042 * (CWT/1.92)^0.909 * exp(η[3])	Cl = 34.93% V = 21.33% Q = 50.59% Additive error – 0.283 mg/L Proportional error – 50.7%

M8	CL = 0.093 * (CWT/1.92)^1.1 * (PNA/28)^0.299 * exp(η[1]) Vc = 0.637 * (CWT/1.92)^1.03 * exp(η[2]) Vp = 0.480 Q = 0.051 * (CWT/1.92)^0.995 * exp(η[3])	Cl = 41.83% V = 19.57% Q = 71.34% Additive error – 0.318 mg/L Proportional error – 50%
M9	CL = 0.153 * (BWT/2.5)^1.31 V = 2.94 * (BWT/2.5)^1.18	Cl = 58.9% V = 50.7% Residual proportional variability = 46.1%
M10	CL = 0.23 * (CWT/2)^0.691 * (PMA/40)^3.23 * exp(η[1] V = 0.957 * (CWT/2)^0.89 * exp(η[2])	
M11	CL = 0.066 * (BWT/2.285)^1.30 * (1+0.302*(PNA/2)) * 0.846^(Ibuprofen) * exp(η[1]) Vc = 1.03 * (CWT/2.1)^0.863 Q = 0.480 * CL Vp = Vc	Cl = 30.34% Residual Proportional error = 4.48% Additive error = 0.315
M12	Ke = 0.19 * exp(η[1]) V = 0.55 * WT * exp(η[2]) CL = 103 * WT	

- Cl - clearance; V – volume of distribution; Vc – volume of central compartment; Vp – volume of peripheral compartment; Q – inter compartmental clearance; Ke – elimination rate compartment; PNA – postnatal age; PMA – post menstrual age; SCr – serum creatinine; CrCl – creatinine clearance; WT,CWT – current body weight; BWT – birth weight; PCA – post conception age;
- Total of twelve models were extracted from eleven published studies. Illamola et al has published two different models, using CrCl and PNA as covariates on cl of amikacin.