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Dosing regimen of gentamicin in neonates: evaluation of current guidelines based on a large population pharmacokinetic analysis

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Objectives: Gentamicin is among the most commonly prescribed antibiotics in newborns, but large interindividual variability in exposure levels exists. Based on a population pharmacokinetic analysis of a cohort of unselected neonates, we aimed to validate current dosing recommendations from a recent reference guideline (Neofax®).

Methods: From 3039 concentrations collected in 994 preterm (median gestational age 32.3 weeks, range 24.2-36.5) and 455 term newborns, treated at the University Hospital of Lausanne between 2006 and 2011, a population pharmacokinetic analysis was performed with NONMEM®. Model-based simulations were used to assess the ability of dosing regimens to bring concentrations into targets: trough ≤ 1mg/L and peak ~ 8mg/L.

Results: A two-compartment model best characterized gentamicin pharmacokinetics. Model parameters are presented in the **table**

Table. Parameters estimates of final model

Parameters	Estimates (SE%)	BSV (%)
CL (L/h)	0.089 (1%)	28 (3%)
θ_{CLBW}	0.75 (-)	
θ_{CLGA}	1.870 (4%)	
θ_{CLPNA}	0.054 (6%)	
θ_{CLDOPA}	-0.120 (22%)	
V_c (L)	0.908 (2%)	
θ_{VcBW}	1 (-)	18 (1%)
θ_{VcGA}	-0.922 (8%)	
Q (L/h)	0.157 (7%)	
θ_{CLBW}	0.75 (-)	
V_p (L)	0.560 (4%)	
θ_{VpBW}	1 (-)	
Correlation CL-V_c (%)	86 (3%)	
Additive residual error (mg/L)	0.1	
Proportional residual error (%)	17.8	

[a] Standard errors of the estimates (SE), defined as SE/estimate and expressed as percentages

[b] Standard errors of the coefficient of variation, taken as SE /(estimates x 2) and expressed as percentage

CL = Clearance; **V_c** = Central volume of distribution; **BW**= Body weight; **GA** = Gestational age; **PNA** = Postnatal; **DOPA** = Dopamine; **Q** = Intercompartmental clearance; **V_p** = Peripheral volume of distribution; **BSV** = Between subject variability

[Parameters estimates of final model]

. Body weight, gestational age and postnatal age positively influence clearance, which decreases under dopamine administration. Body weight and gestational age influence the distribution volume. Model based simulations confirm that preterm infants need doses superior to 4 mg/kg, and extended dosage intervals, up to 48 hours for very preterm newborns, whereas most term newborns would achieve adequate exposure under 4 mg/kg q. 24 h. More than 90% of neonates would achieve trough concentrations below 2 mg/L and peaks above 6 mg/L following most recent guidelines.

Conclusions: Simulated gentamicin exposure demonstrates good accordance with recent dosing recommendations for target concentration achievement.

Assigned speakers:
PharmD Aline Fuchs , Centre Hospitalier Universitaire Vaudois and University of Lausanne , Lausanne , CH

Assigned in sessions:
15.05.2014, 08:30-17:30, Posters, General Internal Medicine II, Poster Area
15.05.2014, 10:15-12:00, Invited Societies, Guest Society - SGKPT: Oral Poster Presentation Session, Room E