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Population pharmacokinetic study to evaluate dosing strategies of imipenem in neonates and infants

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OBJECTIVES

Imipenem is a broad spectrum antibiotic used to treat severe infections in critically ill patients. Objectives were:

- ⇨ to identify key **demographic** and **clinical factors** influencing imipenem exposure in **neonates** and **infants**
- ⇨ to assess **dosing regimens** to maintain drug concentration for at least **40% of the time above the minimum inhibitory concentration (T>MIC)** of most common microorganisms encountered (EUCAST: http://mic.eucast.org/Eucast2/)
- ⇨ to establish **reference values** for the monitoring of imipenem concentration in neonates and infants

METHODS

- Data were collected from a cohort of unselected neonates and infants with at least one imipenem concentration measured between 2002 and 2013, upon the physician decision within a Therapeutic Drug Monitoring (TDM) program, in the Neonatal Intensive Care Unit of the Lausanne University Hospital
- The population pharmacokinetic (PK) analysis was performed using non-linear mixed effect modeling (NONMEM®)
- From the final model, 10 000 cycles of simulation were performed to generate concentration-time profiles for various dosing regimens (from **15 to 35 mg/kg every 6h [Q6], 8h [Q8], 12h [Q12], and 24h [Q24]**). The probability of target attainment (PTA) was calculated for MIC ranging from 0.125 to 32 mg/l.

Patients	Median (range) or count (%)	
Total	68	
Gender (male / female)	32	(47%) / 36 (53%)
Gestational Age (weeks)	27.3	(24.3 – 41.4)
Postnatal Age (days)	21	(2 – 153)
Body Weight (kg)	1195	(0.500 – 4.120)
Plasma creatinine (µmol/l)	46	(9 - 243)
Concentrations		
Total	144	
BLQ (< 0.01 mg/L)	22	(15%)
Trough (count / value (mg/l))	102	(71%) / 1.2 (0.1 – 8.2)
Peak (count / value (mg/l))	42	(29%) / 21.1 (7 – 57.9)
Current dosage (mg/kg)	20	(12 - 30)
Medication		
Furosemide	16	(24%)
Spironolactone	5	(7%)
Hydrochlorothiazide	5	(7%)
Vancomycine	41	(60%)
Diagnosis		
Empirical treatment	44	(65%)

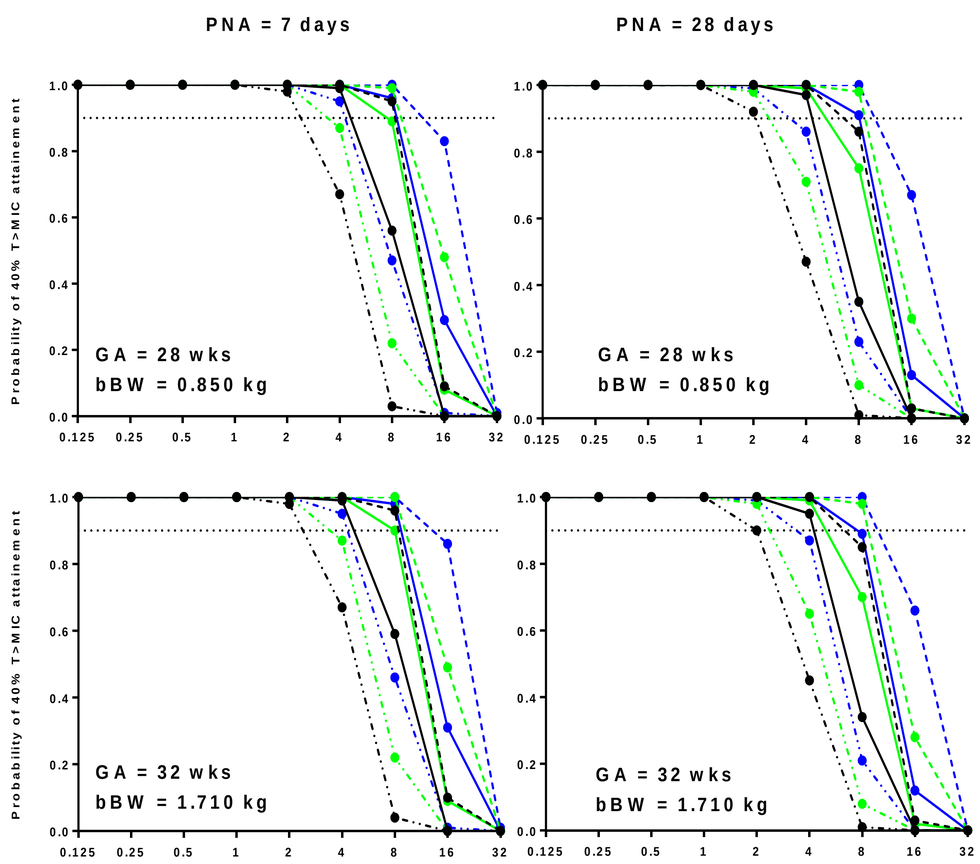
RESULTS

- Imipenem disposition was adequately described by a 2-compartment model. Actual **body weight** explained 19% of inter-individual variability in CL, **gestational age** 9%, **postnatal age** 14% and **serum creatinine** 9%.

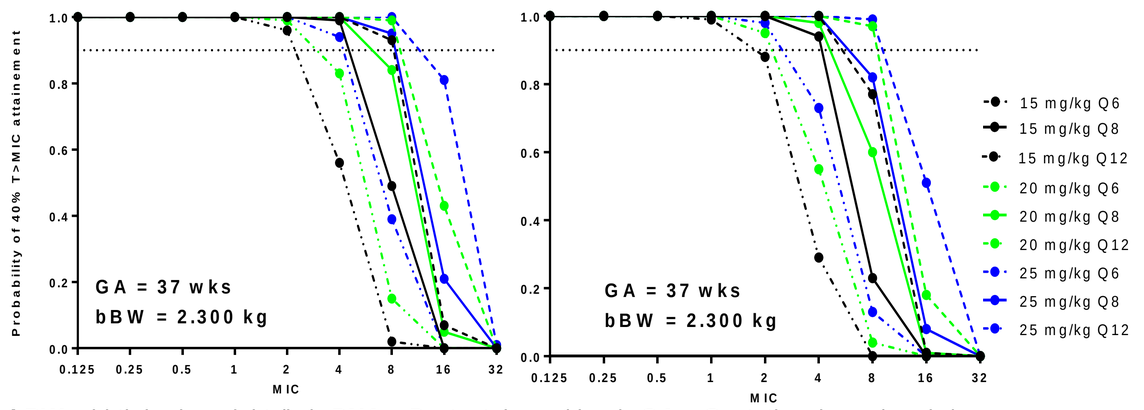
CL	*Total clearance*
BW	*Actual body weight (kg)*
PNA	*Postnatal age (weeks)*
GA	*Gestational age (weeks)*
CRT	*Plasma creatinine (µmol/l)*
Vc	*Central volume of distribution*
Q	*Intercompartmental clearance*
Vp	*Peripheral volume of distribution*
IIV	*Inter-individual variability*

Parameters (units)	Base parameter estimates (SE)	Final parameter estimates (SE)
CL (L/h/kg$^{0.75}$)	0.31 (34.7%)	0.27 (10.1%)
Effect of BW on CL		0.75
Effect of PNA on CL		0.07 (31.8%)
Effect of GA on CL		0.02 (22.7%)
Effect of CRT on CL		-0.20 (39.4%)
Vc (L/kg)	0.52 (46.2%)	0.57 (7.8%)
Effect of weight on Vc		1
Q (L/h/ kg$^{0.75}$)	0.08 (26.5%)	0.05 (39.0%)
Effect of BW on Q		0.75
Vp(L/kg)	0.43 (59.0%)	0.18 (27.3%)
Effect of weight on Vp		1
IIV CL (% CV)	43 (5.0%)	21 (15.7%)
Residual error (% CV)	47 (7.0%)	37 (6.3%)

$$CL = 0.27 \times BW^{0.75} \times (1 + 0.02 \times (GA - 40)) \times (1 + 0.07 \times PNA) \times \left(\frac{CRT}{50}\right)^{-0.2}$$



- Model-based simulation suggested that 15 mg/kg every 12h would maintain drug concentration over a MIC = 2 mg/l for at least 40% of the time in most neonates. Infants (> 28 days of life) born after 32 weeks of gestation required higher doses to achieve higher PTA, i.e 20 mg/kg every 12h. Higher MIC (4 mg/l) required dividing the daily dose into 3 administrations per day, i.e. 15 mg/kg every 8h.
- Maintaining concentration 100% T > MIC in case of severe infection has also been advocated. Simulations showed that it would required administration 4 times a day with doses ranging from 15 mg/kg to 25 mg/kg according to age *(data not shown).*



bBW *= birth body weight (kg);* ***PNA*** *= Postnatal age (days);* ***GA*** *= Gestational age (weeks); dotted line = represents 90% probability of attaining 40% T > MIC*

Conclusion

- ☞ Dosing strategies based on body weight and post-natal age are recommended for imipenem in all critically ill neonates and infants.
- ☞ Most current guidelines seem adequate for newborns considering a MIC of 2 and a target of 40% T > MIC. Higher MIC and higher T > MIC target require dividing and increasing daily dosages. TDM may be of interest in particular clinical situations.
- ☞ Renal impairment and infusion time should be considered in further simulations.