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

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)** considering specific MIC[1].

⇨ to establish reference values for the monitoring of imipenem concentration in this population.

METHODS

- Data were collected from a cohort of unselected neonates and infants between 2002 and 2013 in the Neonatal Intensive Care Unit of the Lausanne University Hospital. Patients were included if at least one imipenem concentration was measured upon the physician decision within a Therapeutic Drug Monitoring (TDM) program.
- 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 was calculated for MIC ranging from 0.125 to 32 mg/l.

Patients (n = 68)	Median (range) or count (%)	
Gender (male)	32	(47%)
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 (n = 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)
Dose before concentration (mg/kg)	20	(12 - 30)
Medication		
Furosemide	16	(24%)
Spironolactone	5	(7%)
Hydrochlorothiazide	5	(7%)
Vancomycine	41	(60%)
Diagnosis		
Empirical treatment	44	(65%)

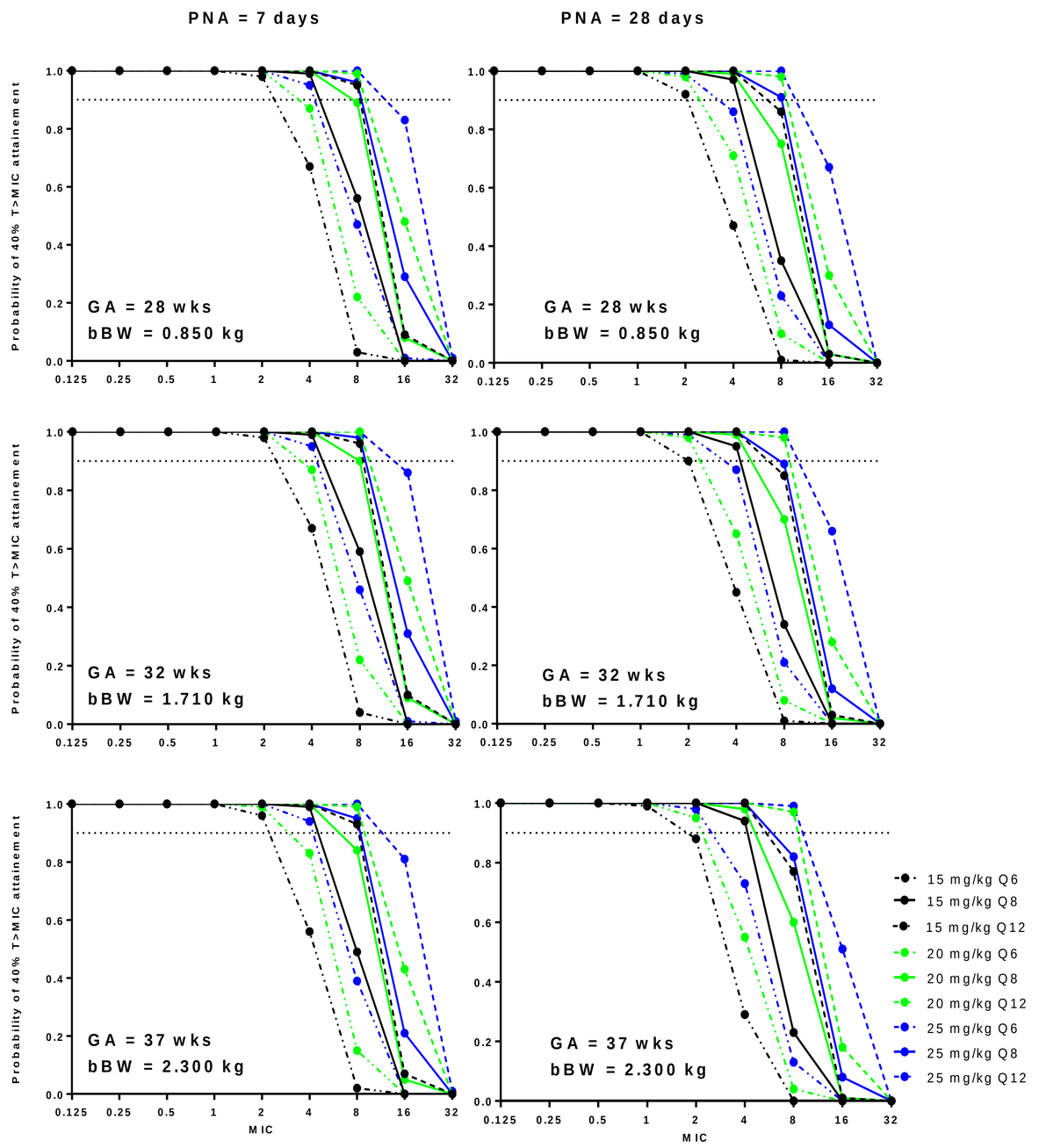
RESULTS

- 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 renal function reflected by **serum creatinine** 9%.

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%)

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

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*
SE *Standard Error*



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

- 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 probability of target attainment, i.e 20 mg/kg every 12h. Target attainment considering microorganisms with higher MIC (4 mg/l) requires to divide 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 require administration 4 times a day with doses ranging from 15 mg/kg to 25 mg/kg according to age (gestational and postnatal age) *(data not shown).*

Conclusion

☞ Dosing strategies for imipenem in all critically ill neonates and infants should be based on body weight and age.

☞ Most current guidelines seem adequate for newborns considering a MIC of 2 mg/l and a target of 40% T > MIC. Higher MIC and higher T > MIC target require dividing and increasing daily dosages.

☞ Renal impairment and infusion time exceeding 30 minutes should be considered in further simulations.

References

[1] EUCAST: http://mic.eucast.org/Eucast2/