Population pharmacokinetics of imipenem bone concentrations in pigs

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INTRODUCTION

- Imipenem (IPM) is a broad-spectrum β-lactam antibiotic frequently used in intensive care units to treat nosocomial infections and BGN infections.
- It allows to treat severe infections of all body systems notably bone infections.
- Interestingly, IPM is a good drug candidate for microdialysis studies (fig 1).

The objective of the present study was to investigate the bone distribution of IPM by microdialysis in healthy pigs in order to extrapolate to human.

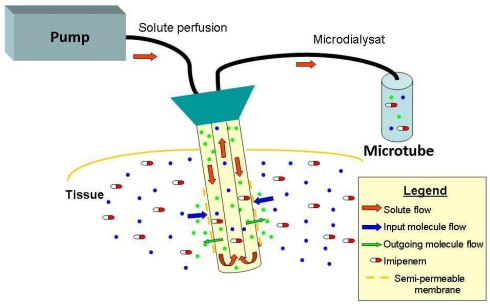


Figure 1 : Microdialysis concept

METHOD

- **8** healthy pigs (26-30kg) were included.
- An **arterial** catheter and a **medullar bone** microdialysis (figure1) probe were inserted in the left posterior tibia after a general anesthesia.
- Pigs received an intravenous infusion of 15mg/kg of IPM over a 30 min period.
- **Blood** samples and **bone** dialysates were collected at 5, 15, 30, 45, 60, 120, 180, 240 and 300 min following infusion.
- IPM concentrations in **plasma** and **microdialysat** were determined by a validated HPLC method with UV-VIS detection (Dionex detector UVD170U).
- The in vivo recovery of the microdialysis was evaluated by retrodialysis (63%).
- Data were analysed using the non linear mixed effect modeling software program NONMEM (version VI.2).
- Plasma and bone concentrations were described using the nonmem subroutines ADVAN3 and ADVAN11.

RESULTS

- A 3-compartments model best described the whole dataset (table 1 - figure 2) . Bone and plasma concentrations are represented on figure 3 and 4.
- The model of pharmacokinetic in pig was validated using a bootstrap analysis and goodness of fit plots with normalized predictive distribution error.
- Human bone concentrations were simulated using the pig constant rates between plasma and bone, together with a published model in HV. 3 doses imipenem were tested : 250mg, 500mg and 750mg (figure 5).

Figure 2 : The PK model.

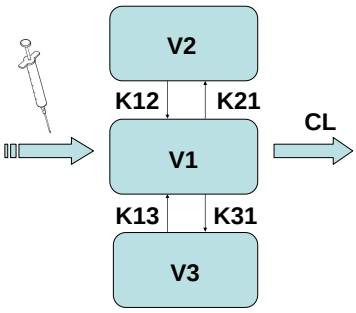


Table 1 : Final estimates for population PK parameters of imipenem in pigs.

	Value	se (%)	IC 95 Lower	IC 95 higher
PK parameters				
CL (L/h)	7.08	13.3	5.57	10.62
V1 (L)	2.56	7.70	2.20	3.07
Q (L/h)	3.43	18.0	2.59	5.44
V2 (L)	2.59	9.90	2.18	3.21
K13 (1/h)	0.21	45.0	0.11	0.43
K31(1/h)	2.46	23.0	1.63	3.27
InterIndividual Variability				
ω CL (%)	22	44	10.20	44.30
ω K13 (%)	61	25	4.86	69.60
Residual variability				
ε prop Plasma (%)	22	33	14.00	29.30
ε prop Bone (%)	37	43	16.20	41.90

Figure3: Observed plasma concentrations of IPM (DV) versus predicted concentrations (PRED).

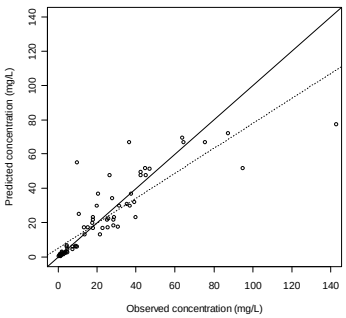


Figure4: Observed bone concentrations of IPM (DV) versus predicted concentrations (PRED).

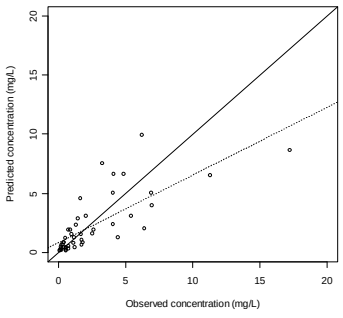


Table2 : NONMEM plasma results in healthy pigs compared to healthy human parameters.

PK parameters	Pigs (30kg)	Healthy Volunteers [1]
CL (L/h/kg)	0.25	0.17+/-0.02
V1 (L/kg)	0.085	0.16+/-0.04
V2 (L/kg)	0.086	0.07
Vss (L/kg)	0.17	0.23+/-0.03
k12 (1/h)	1.34	0.98+/-0.20
k21 (1/h)	1.32	1.73+/-1.11

CL = total clearance

V1 =central volume of distribution

Q =intercompartmental clearance

V2= peripheral volume of distribution

K12 = first order intercompartment rate constant from central to peripheral compartment

K21 = first order intercompartment rate constant from peripheral to central compartment

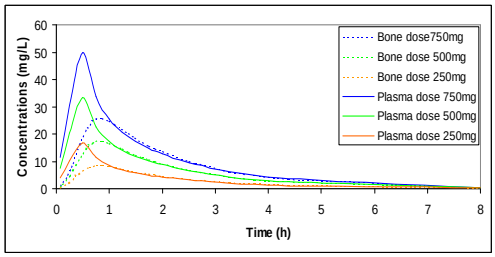
K13 = first order intercompartment rate constant from central to bone compartment

K31 = first order intercompartment rate constant from bone to the central compartment

V3 = bone volume of distribution

Vss = volume of distribution at steady state

Figure 5 : Simulated bone concentrations of IPM in human based on a pig model with 3 differents doses.



CONCLUSION

- The estimation of total clearance (0.25 L/h/kg) and volume of distribution (0.17 L/kg) in pigs are in agreement with those obtained in human (0.17 L/h/kg and 0.23 L/kg). These parameters are of interest because imipenem is a time-dependent antibiotic (Time above MIC > 4mg/L).
- Our model can be used to predict plasma to bone transfert of IMP in human with the hypothesis that the process are similar between the 2 species.
- The simulations show that bone concentrations decrease below the MIC within the 8h requiring 3-4 administrations per day.
- Our pig model with microdialysis is a useful tool for evaluation of the bone concentrations and allows extrapolation to human.

Reference:

[1] Standiford, H.C., et al., Imipenem coadministered with cilastatin compared with moxalactam: integration of serum pharmacokinetics and microbiologic activity following single-dose administration to normal volunteers. Antimicrob Agents Chemother, 1986. ***29****(3): p. 412-7.*