TOWARDS PREDICTING HUMAN INNER EAR PHARMACOKINETICS: ALLOMETRIC SCALING USING GUINEA PIGS AND SHEEP

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INTRODUCTION

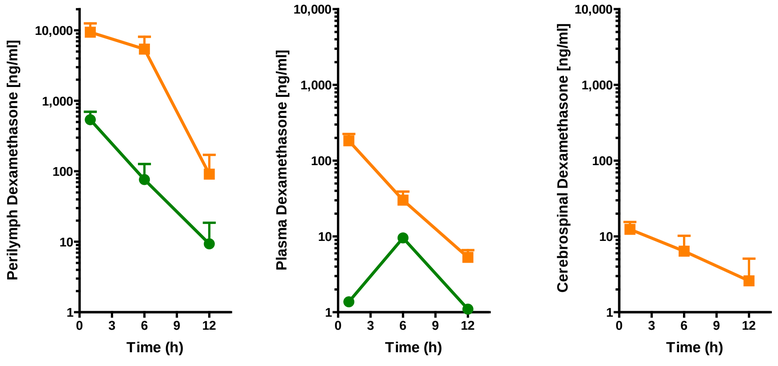
Projecting drug levels in humans from pharmacokinetic studies performed in animals is a critical component of drug development. In particular, this exercise provides useful information to the assessment of efficacy and safety profiles of the drug candidate under development. Typically, the pharmacokinetic evaluation of a drug candidate includes pharmacokinetic studies in multiple species, including both small and large mammals. Pharmacokinetic parameters obtained in animals are then scaled to human using various approaches, most commonly in a process known as allometric scaling. To date, there are no published studies on allometric scaling as applied to inner ear pharmacokinetics.
Among large mammals, the middle and inner ear structures of pigs and sheep are closely related to the human ear. In particular, comparative and morphometric studies using CT-scan and electron microscopy technologies have demonstrated that the middle and inner ear compartments of sheep and pigs are anatomically and functionally similar to that of humans. However, tissue thickness and bony protrusions in the ear structures of pigs makes it a more technically challenging model. The sheep, in which most structures maintain a 2/3 ratio to the human ear and by extension a 6-7 to 1 ratio with guinea pig, thus constitutes the most acceptable and practical model. In this study, the feasibility of considering the sheep as a model for middle ear drug delivery and inner ear pharmacokinetics was explored. An attempt at colleting preliminary information on the inner ear pharmacokinetic profile of dexamethasone in guinea pigs and sheep, following intratympanic administration of a dexamethasone sodium phosphate (DSP) solution or a dexamethasone-loaded poloxamer hydrogel (OTO-104), was made.

METHODS

Female guinea pigs (Charles River) weighing 200-300g, of approximately 6-8 weeks of age were used (N = 4 per time point). *Intratympanic injection* – Each animal was positioned so that the head was tilted at an angle to favor injection towards the round window niche. Briefly, under visualization with an operating microscope, 50 µl of the formulation was injected using a 27G or 30G needle through the tympanic membrane into the superior posterior quadrant behind which the round window niche is located. Perilymph (5 µl) was collected from the base of the cochlea.

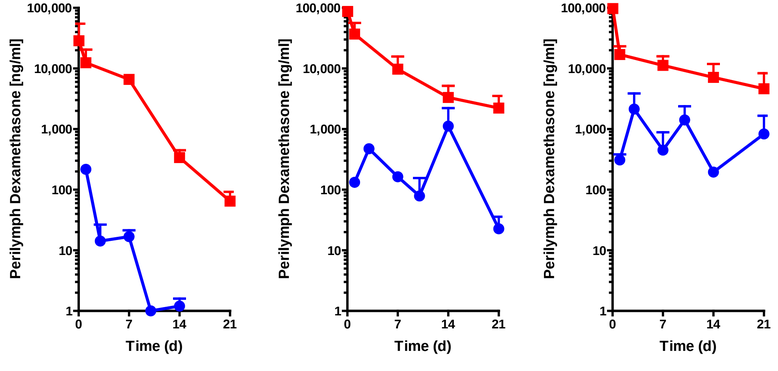
Female sheep (Buckham Sheep Farm, Kalamazoo, MI) weighing 50-65kg, of approximately 2-4 years of age were used (N=1, 2 ears per time point). *Intratympanic injection* – Each intubated animal was immobilized and placed laterally in reverse trendelenburg position, with the rostrum slightly elevated to ensure access to the round window. Following ear cleaning and under otoscopic visualization, 600 µl of the formulation was injected using a 25G or 27G needle through the tympanic membrane into the posterior inferior quadrant towards the round window niche. After dosing, the animal was left on an incline with its head up for approximately 30min to allow the dosing solution to settle into the tympanic cavity. Procedure was then repeated for the opposite ear. Perilymph (50µl) was collected from the base of the cochlea. Sheep studies were performed at MPI Research, Kalamazoo, MI.

PHARMACOKINETICS OF 2% DSP SOLUTION



Metric	Guinea pig			Sheep		
	PL	P	CSF	PL	P	CSF
Cmax (µg/mL)	9.40	0.18	0.01	0.54	0.01	<0.01
AUC (µg.h/mL)	57.0	0.8	0.1	2.4	0.1	0.01
MRT (h)	3.6	2.4	-	2.1	-	-

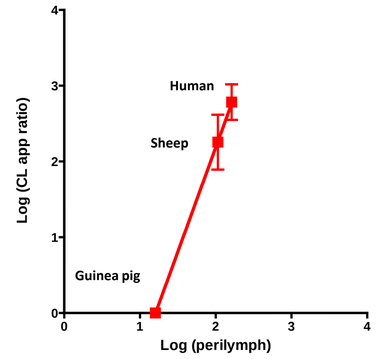
INNER EAR PHARMACOKINETICS OF OTO-104



Metric	Guinea pig			Sheep		
	OTO-104			OTO-104		
	2%	6%	20%	1.5%	6%	20%
Cmax (µg/mL)	28.7	87.3	97.5	0.2	0.5	2.1
AUC (µg.h/mL)	2492	6979	7763	13	102	389
MRT (h)	90	136	302	43	153	220

ALLOMETRIC SCALING

Metric	Guinea pig				Sheep				GP	Human	
	DSP	OTO-104			DSP	OTO-104			MPred	MPred	
	1.5%	2%	6%	20%	1.5%	1.5%	6%	20%	[1]	[2]	[3]
Dose (µg)	750	1,000	3,000	10,000	9,000	9,000	36,000	120,000	5,000	22,700	22,700
AUC (µg.h/mL)	57	2,492	6,979	7,763	2.4	13	102	389	6,722	21.8	40.0
CLapp (mL/h)	13.2	0.4	0.4	1.3	3,750	692	353	309	0.8	1,040	568



CLapp: Apparent clearance (Dose / AUC); CLapp ratio is normalized to the guinea pig (guinea pig = 1).
Perilymph volumes are 16 µl in guinea pig, 159-166 µl in humans, and by extrapolation 106-111 µl in sheep (2/3 of human) .
[1] : Bachmann et al, 2001. Permeability of the RWM for prednisolone-21-hydrogen succinate. HNO 49:538-42.
[2] : Bird et al, 2007. Intratympanic vs intravenous delivery of methylprednisolone to cochlear perilymph. Otol Neurotol 28:1124-30.
[3] : Plontke et al, 2008. Rapid clearance of methylprednisolone after intratympanic application in humans. Otol Neutotol 29:732-3.

CONCLUSIONS

* Sheep is a practical and acceptable model to study inner ear pharmacokinetics in large mammals.

* Administration of OTO-104 in sheep is associated with lasting exposure in the perilymph (> 3 weeks).

* Dexamethasone inner ear exposure is significantly lower in sheep than in guinea pigs:
  - with DSP solution, 17-24 fold difference,
  - with OTO-104 hydrogel, 20-200 fold difference depending on the dose administered.

* In both guinea pigs and sheep, systemic exposure is minimum (plasma and CSF).

* Preliminary allometric scaling analysis is projecting:
  - a 3-order magnitude difference in inner ear exposure between guinea pigs and humans,
  - a half log difference between sheep and humans.