Population Pharmacokinetics of ZT-1 and its Active Metabolite Huperzine A after Intravenous, Oral and Subcutaneous Administration in Healthy Volunteers

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Background

ZT-1 is currently in development for the treatment of mild to moderate Alzheimer's disease. ZT-1, through its active metabolite huperzine A (Hup A), has been shown to be a potent and selective inhibitor of acetylcholinesterase in vitro and in vivo.

This study aimed at characterizing the pharmacokinetic (PK) profile of ZT-1 and to describe the biotransformation of ZT-1 into Hup A after administration of intravenous, oral and subcutaneous doses.

Method

Studies : 5 single dose phase I studies and 1 multiple dose phase I study over 14 days

Patients : 88 healthy young and elderly healthy volunteers

Data : 2425 plasma concentrations of ZT-1 and 2679 of Hup A. Rich sampling design (average 19 ±7.6 plasma concentration measurements per individual)

Doses : 3 routes of administration of ZT-1: iv (0.1, 0.3 mg), po (0.5, 1, 1.5, 2 and 3 mg) and sc (0.3, 0.6 mg)

Analytical Methods : Plasma measurement of ZT-1 and Hup A by LC/MS/MS

PK Analysis : multi-compartment model using NONMEM (Version V), subroutine ADVAN6, using FOCE CENTERING

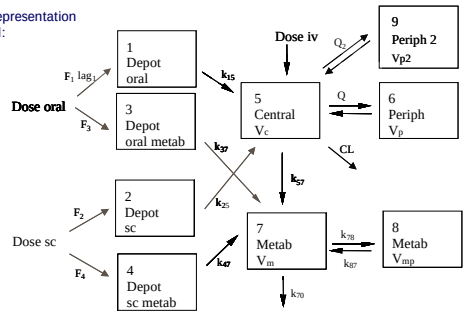
Covariates analysis : generalized additive model and diagnostic plots to evaluate the potential influence of specific covariates : demographic covariates (body weight, height, sex, age, body mass index), food intake, creatinine clearance

Error model : log normal error distribution for the intersubject variability in the pharmacokinetic parameters and log normal and additive error model for the intrasubject variabily.

Results

- A three compartment model adequately fitted ZT-1 plasma concentration data for oral, iv, and sc routes, with first-order absorption for oral and sc doses and first-order elimination as illustrated in Figure 1.
- A first order biotransformation of ZT-1 to Hup A was used to fit the metabolite data, for which a bicompartimental disposition was observed (Figure 1).
- ZT-1 underwent both a systemic and a presystemic metabolisation into HuP A. Approximatively 30% of the oral and 65% of the sc ZT-1 doses were transformed directly into the active metabolite in the absorption compartments.
- An increase in the bioavailability of ZT-1 was observed after intake of the 2 mg and the 3 mg oral doses. A reduction of ZT-1 bioavailabilility was observed between the 0.3 and the 0.6 mg sc doses.
- No covariates seemed to affect ZT-1 pharmacokinetics nor Hup A in this group of healthy volunteers.

Schematic representation of the model:



with $F_1 = e^{\theta_1}/(1+e^{\theta_1})$ $F_2 = e^{\theta_3}/(1+e^{\theta_3})$

$F_3 = (1-F_1)\theta_2$ $F_4 = (1-F_2)$

where $\theta_{1\text{-}3}$ are population parameter estimates

Pharmacokinetic Parameter Estimates of ZT-1 and Hup A

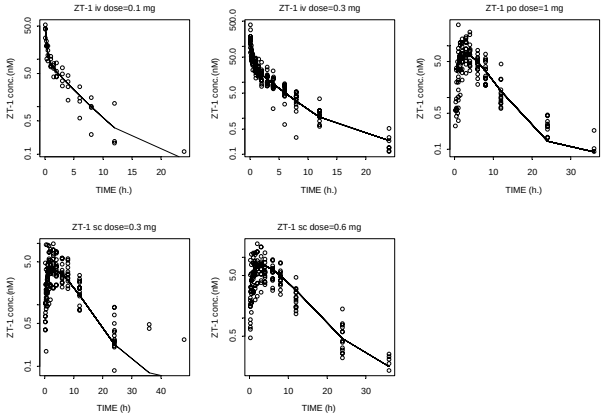
ZT-1 PK parameters	Population estimates	IIV CV %	Hup A PK parameters	Population estimates	IIV CV %
CL (L/h)	6.53	48	k57 (h^{-1})	5.0	
V_c (L)	1.41	66	k70 (h^{-1})	10.6	
V_p (L)	11.8	19	k78 (h^{-1})	124	42
Q (L/h)	19		k87 (h^{-1})	0.54	50
V_{p2} (L)	32.7	73	V_m (L)	1 fixed	
Q_2 (L/h)	1.45		V_{mp} (L)	1 fixed	
k_{15} (h^{-1})	0.39	27	k37 (h^{-1})	0.57	
Lag_1 (h)	0.46		k47 (h^{-1})	0.134	33
k_{25} (h^{-1})	0.19	42			
F_{sc} (0.3 mg)	0.36	F_2 14	F_{scm} (0.3 mg)	0.64	(F_4) 14
F_{sc} (0.6 mg)	0.27		F_{scm} (0.6 mg)	0.73	
F_{oral} (0.5, 1 mg)	0.14	F_1 57	F_{oralm} (0.5,1 mg)	0.36	(F_3) 57
F_{oral} (2 mg)	0.17		F_{oralm} (2 mg)	0.31	
F_{oral} (3 mg)	0.25		F_{oralm} (3 mg)	0.34	
σ add (nM)	0.52		σ add (nM)	0.39	
σ prop (CV%)	25		σ prop (CV%)	30	

IIV: inter individual variability, σ: intraindividual variability, add: additive error model, prop: proportional error model

Derived Pharmacokinetic Estimates of ZT-1 and Hup A

ZT-1		Hup A	
t ½ α (h)	0.03	t ½ β (h)	0.39
t ½ β (h)	1.5	t ½ γ (h)	18
t ½ γ (h)	19		
t ½ ka oral (h)	1.8		
t ½ ka sc (h)	3.6		
Vd_{ss} (L)	45.9		

ZT-1 concentration-time profiles



Hup A concentration-time profiles

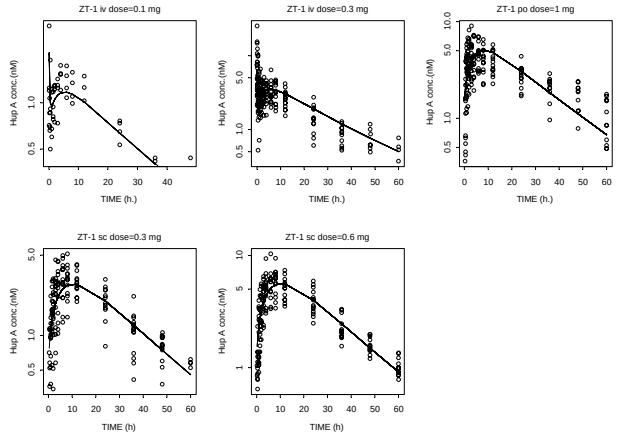


Figure 1. Concentration-time profile of ZT-1 and Hup A (circles) after administration of 0.3, 0.6 mg sc, 1 mg po and 0.1 and 0.3 mg iv ZT-1 with population predictions (solid line) in a representative study [1]

Conclusion

- The combined pharmacokinetics of ZT-1 and Hup A are adequately described using the 9-compartment model after three routes of administration (iv, po, sc).
- The parameter estimates indicate that ZT-1 is rapidly transformed into Hup A via both a presystemic and central biotransformation.
- About 65 % of the sc dose and 30 % of the oral doses of ZT-1 are transformed directly into Hup A in the absorption compartments.
- ZT-1 and Hup A elimination is slow with a long terminal half-life of about 19 h., respectively 18 h., which allows a once-daily administration.
- No covariates influence the pharmacokinetic profile of ZT-1 and Hup A in this group of healthy subjects. Further analyses will be performed on the target population of patients.
- This model will be very helpful for further developments of ZT-1.

[1] Ramael S. A study of the pharmacokinetics and safety of an injectable intravenous formulation of ZT-1 in healthy young male and female volunteers (part 1) and of the bioavailability of an oral tablet formulation and of an injectable subcutaneous formulation of ZT-1, as compared to an intravenous formulation, in healthy elderly male and female volunteers (part 2). SGS Biopharma SA, Study DEB-ZT-107, Clinical Study Report; 2004 15 October 2004.