無断転載禁止

Pharmacokinetic modeling for local distribution in rat brain after intranasal administration

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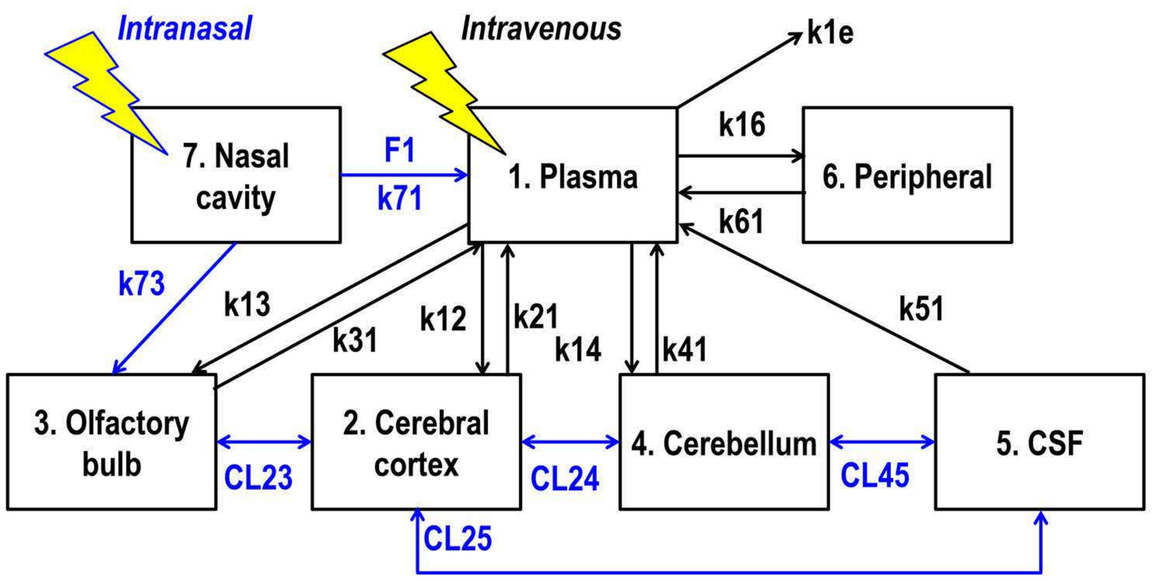
Purpose

We develop a novel pharmacokinetic brain model with diffusion clearance among each part of brain in rats after intranasal administration of ranitidine as a model compound, in order to evaluate local distribution of a compound in brain after intranasal administration quantitatively.



Materials and Methods

Chemicals: Ranitidine hydrochloride

Animals: Male SD rats, 8 weeks old

Dosing regimen: Intravenous (i.v.) and intranasal (i.n.), 3 mg/kg
All animal protocols were approved by the Institutional Animal Care and Use Committee of Takeda Pharmaceutical Company for all animal studies.

Bioanalysis: Concentrations in plasma, cerebrospinal fluid (CSF, collected from cisterna magna), olfactory bulb, cerebral cortex and cerebellum by LC/MS/MS

Modeling software: NONMEM VI (ADVAN6)

Pharmacokinetic model: Sequential fitting from Model 1 to 4

- **Model 1:** Plasma, olfactory bulb, cerebral cortex and cerebellum after **i.v. were fitted**.
- **Model 2:** Plasma, olfactory bulb, cerebral cortex and cerebellum after **i.n. were fitted** with the fixed values at Model 1.
- **Model 3:** Plasma, olfactory bulb, cerebral cortex and cerebellum after **i.v. were re-fitted**, on condition that V1, k1e, k21, k31, k41, k16, k61, CL23 and CL24 were fixed.
- **Model 4:** All the data including CSF after **i.v. and i.n. were simultaneously fitted** with the fixed values at Model 3.

Posterior predictive check: 1000 replications of the simulation in consideration of interindividual variability

Results

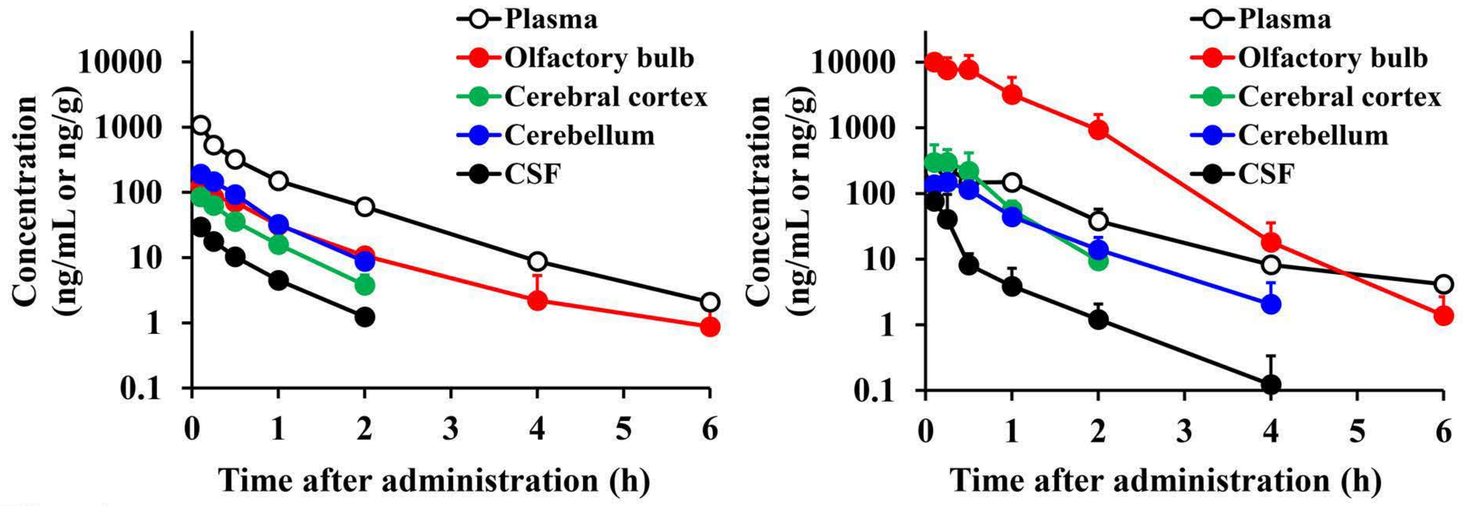


Fig. 1. Concentrations of ranitidine in rat plasma and each part of brain after intravenous and intranasal administrations.

Table I Estimated parameters of ranitidine in rats by modeling

Parameter	Value	SE	CV (%)	LLCI	ULCI	Model
Population mean						
V1 (mL/kg)	2580	260	10.1	2070	3090	1
k1e (1/h)	1.96	0.15	7.6	1.67	2.25	1
k12 (1/1000/h)	1.18	0.23	19.7	0.72	1.64	3
k21 (1/h)	23.4	6.5	27.6	10.7	36.1	1
k13 (1/1000/h)	0.333	0.061	18.3	0.214	0.452	3
k31 (1/h)	8.76	1.77	20.2	5.29	12.20	1
k14 (1/1000/h)	2.40	0.19	7.9	2.03	2.77	3
k41 (1/h)	21.2	6.8	32.2	7.8	34.6	1
k51 (1/h)	126	44	35.1	39	213	4
k16 (1/h)	0.660	0.243	36.8	0.184	1.140	1
k61 (1/h)	1.21	0.20	16.2	0.83	1.59	1
F1	0.671	0.081	12.0	0.513	0.829	2
k71 (1/h)	1.69	0.09	5.1	1.52	1.86	2
k73 (1/1000/h)	23.0	3.9	16.8	15.4	30.6	2
CL23 (mL/h/kg)	1.80	0.51	28.6	0.79	2.81	2
CL24 (mL/h/kg)	20.7	2.7	12.9	15.5	25.9	2
CL45 (mL/h/kg)	6.05	2.83	46.8	0.50	11.60	4
CL25 (mL/h/kg)	13.6	4.8	35.1	4.3	22.9	4
Interindividual variability						
k31	0.177	0.084	47.4	0.013	0.341	1
k51	1.33	0.47	35.3	0.41	2.25	4
Residual variability	0.224	0.059	26.5	0.108	0.340	4

Value: parameter estimate value, SE: calculated standard error, CV: coefficient of variation, LLCI: lower levels for confidence interval, ULCI: upper levels for confidence interval, Model: the number in which model the parameter estimates were obtained.

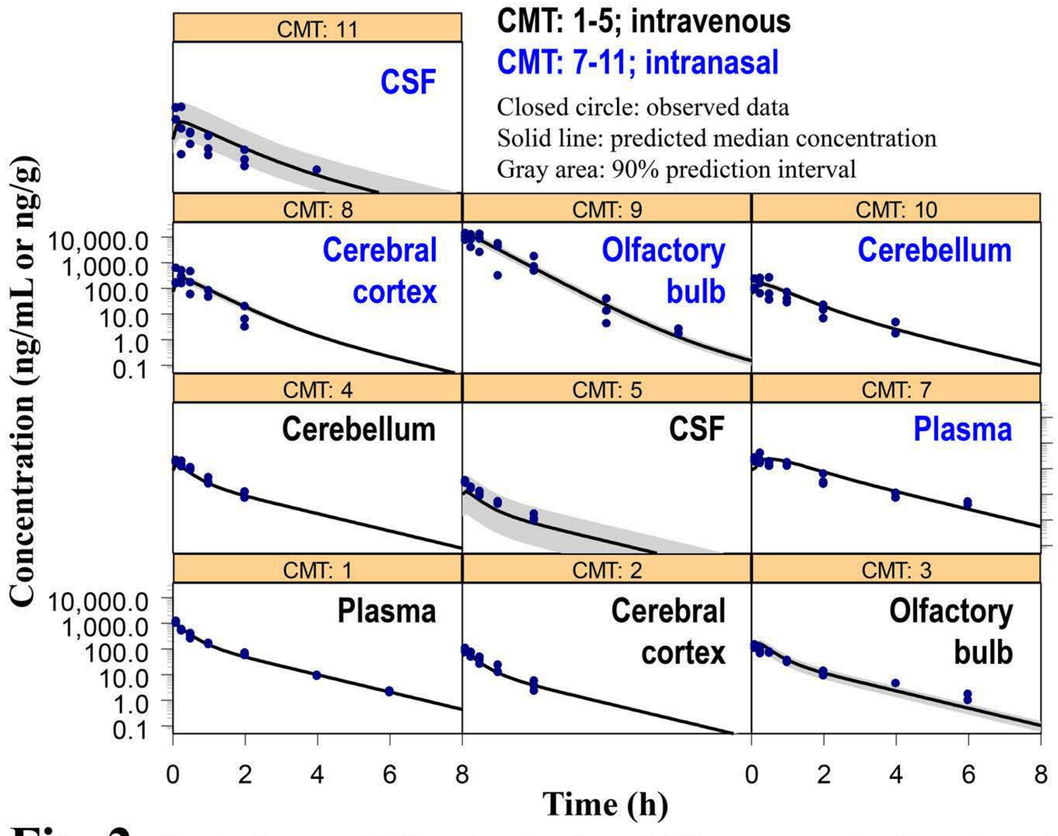


Fig. 2. Posterior predictive check of ranitidine concentrations in rat plasma and each part of brain after intravenous and intranasal administrations.

Table II Model validation

Parameter	Moment analysis	Model analysis
CLtotal (mL/h/kg)	5127	5060
Vd(ss) (mL/kg)	4179	3990
Kp,ob,i.v.	0.18	0.30
Kp,cc,i.v.	0.09	0.05
Kp,cm,i.v.	0.21	0.34
F,i.n.	0.549	0.675

Kp: AUC,tissue / AUC,plasma, ob: olfactory bulb, cc: cerebral cortex, cm: cerebellum, F,i.n.: intranasal bioavailability

Table III Model analysis: Brain exposure via two routes after intranasal administration

Brain part	Exposure route to brain	Amount in brain (% of dose)	
Olfactory bulb	Nose-to-brain	1.34	x 160
	Systemic	8.40×10^{-3}	
Cerebral cortex	Nose-to-brain	5.14×10^{-1}	x 16
	Systemic	3.30×10^{-2}	
Cerebellum	Nose-to-brain	1.22×10^{-1}	x 1.8
	Systemic	6.83×10^{-2}	

Nose to brain: Direct nose-to-brain absorption, systemic: distribution by way of systemic blood after swallowing

The amount in brain after intranasal administration
Direct nose-to-brain absorption > Distribution from systemic blood

Conclusion

A novel pharmacokinetic brain model in rats after intranasal administration was established.

Model analysis indicated that direct nose-to-brain route was dominant for compound exposure in brain.

COI disclosure information

The authors are employees at Axcelead Drug Discovery Partners, Inc. and Takeda Pharmaceutical Company Limited.

We have no financial relationship to disclose for our presentation contents.