A Population Pharmacokinetic Model for Disposition in Plasma, Saliva and Urine of Scopolamine after Intranasal Administration to Healthy Human Subjects

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Introduction: An intranasal gel formulation of scopolamine (INSCOP) was developed for the treatment of Space Motion Sickness. The bioavailability and pharmacokinetics (PK) were evaluated under the Food and Drug Administration guidelines for clinical trials with an Investigative New Drug (IND) protocol. The aim of this project was to develop a PK model that can predict the relationship between plasma, saliva and urinary scopolamine concentrations using data collected from the IND clinical trials with INSCOP.

Methods: Twelve healthy human subjects were administered three dose levels (0.1, 0.2 and 0.4 mg) of INSCOP. Serial blood, saliva and urine samples were collected between 5 min and 24 h after dosing and scopolamine concentrations were measured by using a validated LC-MS-MS assay. Pharmacokinetic Compartmental models, using actual dosing and sampling times, were built using Phoenix (version 1.2). Model selection was based on the likelihood ratio test on the difference of criteria (-2LL) and comparison of the quality of fit plots.

Results: The best structural model for INSCOP (minimal -2LL= 502.8) was established (Figure 1). It consisted of one compartment each for plasma, saliva and urine, respectively, which were connected with linear transport processes except the nonlinear PK process from plasma to saliva compartment. The best-fit estimates of PK parameters from individual PK compartmental analysis and Population PK model analysis were shown in Tables 1 and 2, respectively.

Conclusion: A population PK model that could predict population and individual PK of scopolamine in plasma, saliva and urine after dosing was developed and validated. Incorporating a non-linear transfer from plasma to saliva compartments resulted in a significantly improved model fitting. The model could be used to predict scopolamine plasma concentrations from salivary and urinary drug levels, allowing non-invasive therapeutic monitoring of scopolamine in space and other remote environments.

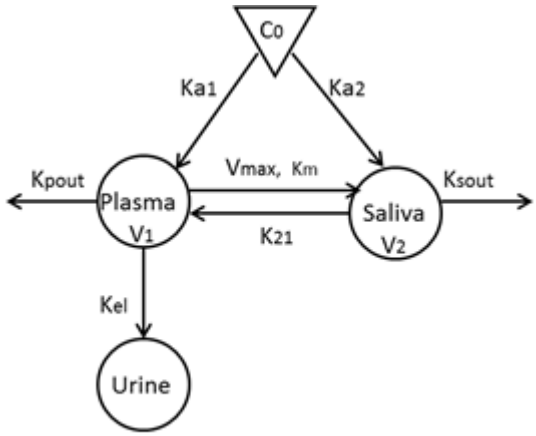

Figure 1. PK Structural Model for INSCOP

Parameter	Unit	Dose=0.1 mg		Dose=0.2 mg		Dose=0.4 mg	
		IND_mean	CV%	IND_mean	CV%	IND_mean	CV%
V1	L	128.00	80.17	212.35	28.51	277.36	87.65
V2	L	40.15	176.29	13.23	82.34	9.57	80.50
Ka1	1/hr	0.31	88.24	0.51	73.54	0.34	39.34
Ka2	1/hr	0.77	99.85	1.05	189.47	0.97	72.07
Vmax	ng/hr	1768.00	121.05	1514.88	74.52	1696.13	137.67
Km	pg/mL	146.72	74.84	120.73	61.82	163.25	67.55
K21	1/hr	1.65	224.49	1.51	184.44	1.23	282.64
Ksout	1/hr	0.40	35.00	0.70	164.81	0.58	108.56
Kpout	1/hr	0.87	68.10	0.66	60.25	0.38	241.53
Kel	1/hr	1.62	61.12	1.02	41.34	0.90	63.59

Table 1. PK Parameters Derived from Individual PK Model Analysis

Parameter	Unit	Dose=0.1 mg		Dose=0.2 mg		Dose=0.4 mg		1000 bootstrap runs	
		Estimate	CV%	Estimate	CV%	Estimate	CV%	Mean	CV%
V1	L	121.00	44.91	182.00	0.08	178.00	45.05	158.00	25.67
V2	L	31.95	29.54	9.78	25.26	9.75	93.54	22.94	91.99
Ka1	1/hr	0.37	20.92	0.34	17.25	0.32	256.68	0.31	64.85
Ka2	1/hr	0.95	30.02	0.97	5.78	0.87	89.98	0.86	76.35
Vmax	ng/hr	1336.00	55.75	1442.00	67.15	1462.78	6.22	1417.70	26.22
Km	pg/mL	119.16	54.20	104.45	66.18	102.49	159.38	98.48	38.99
K21	1/hr	3.64	48.25	3.36	624.00	3.47	481.21	3.51	63.85
Ksout	1/hr	0.53	24.86	0.45	54.79	0.45	108.56	0.52	54.09
Kpout	1/hr	0.54	209.63	0.47	170.49	0.45	374.64	0.52	62.25
Kel	1/hr	0.71	64.70	0.92	80.45	0.85	190.05	0.73	125.13

Table 2. PK Parameters Derived from Population PK Modeling