Pharmacokinetic Modeling of Intranasal Scopolamine in Plasma Saliva and Urine

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ABSTRACT

An intranasal gel dosage formulation of scopolamine (INSCOP) was developed for the treatment of Space Motion Sickness (SMS). The bioavailability and pharmacokinetics (PK) were evaluated under IND guidelines. **The aim** of the project was to develop a PK model that can predict the relationships among plasma, saliva and urinary scopolamine concentrations using data collected from the IND clinical trial protocol with INSCOP. Twelve healthy human subjects were administered at three dose levels (0.1, 0.2 and 0.4 mg) of INSCOP. Serial blood, saliva and urine samples were collected between 5 min to 24 h after dosing and scopolamine concentrations were measured by using a validated LC-MS-MS assay. PK Compartmental models, using actual dosing and sampling time, were established using Phoenix (version 1.2). Model selection was based on a likelihood ratio test on the difference of criteria (-2LL) and comparison of the quality of fit plots.

The results Predictable correlations among scopolamine concentrations in compartments of plasma, saliva and urine were established, and for the first time the model satisfactorily predicted the population and individual PK of INSCOP in plasma, saliva and urine. The model can be utilized to predict the INSCOP plasma concentration by saliva and urine data, and it will be useful for monitoring the PK of scopolamine in space and other remote environments using non-invasive sampling of saliva and/or urine.

BACKGROUND

- An intranasal gel dosage formulation of scopolamine (INSCOP) was developed for space motion sickness (SMS), and bioavailability and pharmacokinetics (PK) were evaluated under approved protocol in IND guidelines.
- Understanding the PK of INSCOP is crucial for the use of this drug in space.
- Pharmacokinetic modeling can be used to describe the PK of INSCOP in plasma as well as in saliva and urine over time.

OBJECTIVE

The aim of this project was to develop a PK model that can describe the relationships among plasma, saliva and urinary scopolamine concentrations, using data collected from the IND clinical trial with INSCOP, and estimate the PK parameters of INSCOP described from a multiple compartmental PK model.

METHODS

Subjects and Treatments:

- Twelve healthy human subjects (6 male/6 female) participated in the study, with an average age of 38.9±8.1 yr., height of 175.6±11.3 cm and weight of 80.8±14.3 kg.
- A randomized double blind crossover study design was used with a seven-day washout period between treatments.
- All subjects were administered at three dose levels (0.1, 0.2 and 0.4 mg) of INSCOP

PK Evaluation

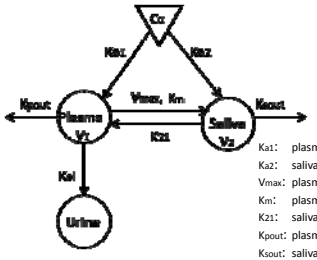
- Serial blood samples (7 ml) were collected at 0, 0.083, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 24 h after each treatment.
- Serial saliva samples (0.4~2 ml) were collected at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 24 hr. after each treatment.
- Urine samples for PK analysis were collected over the following intervals: Pre-dose (single void) and at intervals of 0-3, 3-6, 6-10, 10-12, 12-24 hours.
- Plasma saliva and urine samples were assayed for concentrations of INSCOP using a validated LC/MS/MS method.
- A Waters Acquity UPLC system combined with Micromass Quattro MicroTM API MS/MS detector was used, and concentrations range were between 100 and 1000 pg/mL with LLOQ of 50 pg/mL.

PK Modeling

- Initial estimates of individual compartmental PK parameters were evaluated using Phoenix . Concentrations of Scopolamine (and its glucuronide metabolite) in plasma, saliva and urine were fitted simultaneously.
- Actual dosing and sampling times were used for the compartmental modeling.
- Model discrimination was performed on data using Phoenix, by minimizing the Akaike Information Criteria (AIC) and by comparison of the quality of fit plots (e.g. observed data vs. fitted, weighted residual vs. time).

RESULTS

Figure 1. Best Fit PK Model Structure for INSCOP



Ka1: plasma compartment, absorption rate constant
Ka2: saliva compartment, absorption rate constant
Vmax: plasma to saliva, maximum rate
Km: plasma to saliva, the Michaelis Menten constant
K21: saliva to plasma rate constant
Kpout: plasma compartment, elimination rate constant
Ksout: saliva compartment, elimination rate constant
Kel: plasma to urine rate constant

Table 1. Model Build-Up Summary for Scopolamine

Model No.	Model description	AIC
1p	Plasma, saliva and urine(SCOP and SCOP-G) 1 compartment of plasma; Kps and Ksp for saliva	10275
2p	Plasma, saliva and urine (SCOP) 1 compartment of plasma; Kps and Ksp for saliva	1024.5
3p	Plasma, saliva and urine (SCOP) 1 compartment , Kpout for plasma; Kps and Ksp for saliva	1022.7
4p	Plasma, saliva and urine (SCOP) 1 compartment, Kpout for plasma; Kps,Ksp and Ksout for saliva	976
5p*	Plasma, saliva and urine (SCOP) 1 compartment, Kpout for plasma Ka, Vmax, Km,Ksp and Ksout for saliva	902.7

* Model 5p is the best fit structural model for Scopolamine. It consisted of one compartment each for plasma, saliva and urine, respectively, which were connected with linear transport processes except the nonlinear PK transfer process from plasma to saliva compartment.

Figure 2. Goodness of Fit Plot of Best Fit PK Model(DV – Observed Concentration, IPRED-Individual Predicted Concentration)

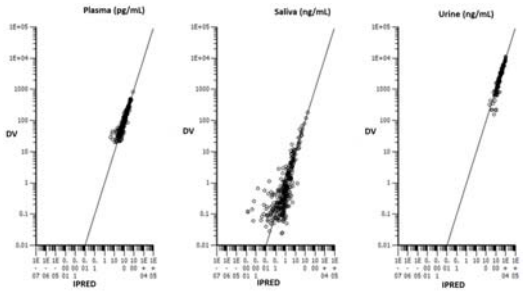


Figure 3. Quality of Fit Plot of Best PK Model(Weighted Residuals versus Time)

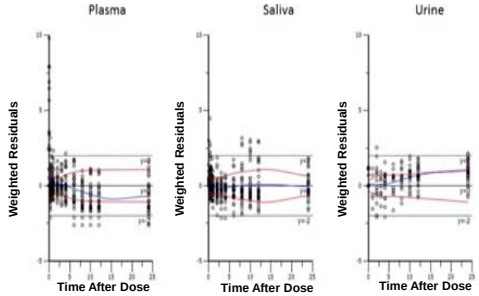


Table 2. The Estimated Values of PK Parameters of INSCOP (Parent Scopolamine) Base on Best Fit PK Model

		Dose (mg)					
		0.1		0.2		0.4	
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%
Ka1	1/hr	0.34	74.3	0.42	69.3	0.37	47.2
Ka2	1/hr	0.72	68.3	0.81	63.2	0.93	57.5
Kpout	1/hr	0.59	43.6	0.69	38.4	0.61	29.7
Kel	1/hr	0.01	24.3	0.01	28.3	0.01	21.6
Ksout	1/hr	0.17	39.8	0.1	40.9	0.12	34.1
Vmax	ng/hr	1698	118.6	1579	89.2	1701	77.8
Km	pg/mL	137.2	71.9	127.7	47.5	158.3	58.4
K21	1/hr	1.57	97.5	1.5	89.5	1.1	84.9
V1	L	597	43.2	821	64.7	639	57.1
V2	L	41.5	87.2	37.4	56.1	29.3	35.4

CONCLUSIONS

- The PK model developed for INSCOP satisfactorily estimated the PK of scopolamine in plasma, saliva and urine after administration.
- The model can be utilized to predict scopolamine plasma concentrations from saliva and urine data, which will be useful for the assessment of PK of scopolamine in space and other remote environments without requiring invasive blood sampling.
- A future objective is to use the validated model to fit data from the bed rest study to predict PK changes of scopolamine after INSCOP administration.

Acknowledgements

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