Pharmacokinetic Modeling of Intranasal Scopolamine in Plasma Saliva and Urine

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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). 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 trial 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 to 24 h after dosing and scopolamine concentrations measured by using a validated LC-MS-MS assay. Pharmacokinetic Compartmental models, using actual dosing and sampling times, were built using ADAPT (version V). Model discrimination was performed, by minimizing the Akaike Information Criteria (AIC), maximizing the coefficient of determination (r^2) and by comparison of the quality of fit plots.

Results: The best structural model for INSCOP (minimal AIC =907.2) was shown in Figure 1. The estimated values of PK parameters were shown in Table 1. The model exercises revealed the nonlinear PK of INSCOP between plasma and saliva compartment in K_{30}, K_{31}, V_{max} and K_m.

Conclusion: PK model for INSCOP was developed and for the first time it satisfactorily predicted the PK of INSCOP in plasma, saliva and urine. The non-linear PK was described in the best structural model between plasma and saliva compartments and the inclusion of non-linear PK resulted in a significant improved model fitting. The model can be utilized to predict the INSCOP plasma concentration by saliva and urine data, which will be useful the assessment of PK of scopolamine in space and other remote environemntswithout requiring invasive blood sampling.

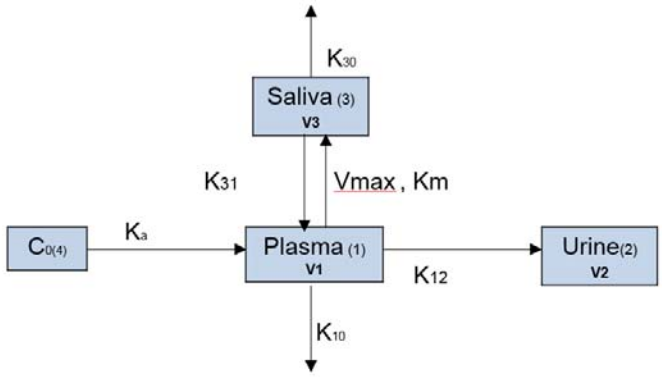

Figure 1

Parameter	Dose(mg)					
	0.1		0.2		0.4	
	Estimate	CV%	Estimate	CV%	Estimate	CV%
$K_{30}(hr^{-1})$	5.8	43.4	2.6	62.3	1.3	33.42
$K_{31}(hr^{-1})$	0.1	30.71	0.07	17.58	0.03	6.93
V_{max}(ng/hr)	0.19	24.2	0.21	38.56	0.11	64.27
K_m(ng/ml)	23.7	36.15	21.6	40.12	11.7	43.4
K_a (hr^{-1})	10.5	21.8	11.13	25.31	10.1	22.48
$K_{10}(hr^{-1})$	0.08	10.86	0.06	12.41	0.07	7.15
$K_{12}(hr^{-1})$	0.26	26.5	0.24	18.73	0.24	11.32

Table 1