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 for 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 Phoenix (version 1.2). 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 to describe scopolamine disposition after INSCOP administration (minimal AIC =907.2) consisted of one compartment for plasma, saliva and urine respectively that were inter-connected with different rate constants. The estimated values of PK parameters were compiled in Table 1. The model fitting exercises revealed a nonlinear PK for scopolamine between plasma and saliva compartments for K_{21}, Vmax and Km.

CONCLUSION

PK model for INSCOP was developed and for the first time it satisfactorily predicted the PK of scopolamine in plasma, saliva and urine after INSCOP administration. Using non-linear PK yielded the best structural model to describe scopolamine disposition between plasma and saliva compartments, and inclusion of non-linear PK resulted in a significant improved model fitting. The model can be utilized to predict scopolamine plasma concentration using saliva and/or urine data that allows non-invasive assessment of pharmacotherapeutics of scopolamine in space and other remote environments without requiring blood sampling.

Description	Parameter	Dose(mg)					
		0.1		0.2		0.4	
		Estimate	CV%	Estimate	CV%	Estimate	CV%
saliva compartment, elimination rate constant	Ksout(hr^{-1})	0.4	35.1	0.7	164.8	0.6	108.6
saliva to plasma rate constant	K_{21}(hr^{-1})	1.7	224.5	1.5	184.4	1.2	282.6
plasma to saliva, maximum rate	Vmax(ng/hr)	1768.0	121.1	1514.9	74.5	1696.1	137.7
plasma to saliva, Michaelis-Menten constant	Km(ng/ml))	146.7	74.8	120.7	61.8	163.3	67.6
plasma compartment, 1st order absorption rate constant	K_a (hr^{-1})	0.3	88.2	0.5	73.5	0.3	39.3
plasma compartment, elimination rate constant	Kpout(hr^{-1})	0.9	68.1	0.7	60.3	0.4	241.5
plasma to urine rate constant	Kel(hr^{-1})	0.01	61.1	0.01	41.3	0.01	63.6

Table 1