Impact of Gender on Pharmacokinetics of Intranasal Scopolamine

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ABSTRACT

Introduction: An intranasal gel dosage formulation of scopolamine (INSCOP) was developed for the treatment of Space Motion Sickness (SMS), which is commonly experienced by astronauts during space missions. The bioavailability and pharmacokinetics (PK) were evaluated under IND guidelines. Since information is lacking on the effect of gender on the PK of Scopolamine, we examined gender differences in PK parameters of INSCOP at three dose levels of 0.1, 0.2 and 0.4 mg.

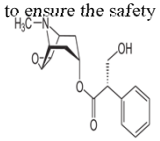
Methods: Plasma scopolamine concentrations as a function of time data were collected from twelve normal healthy human subjects (6 male/6 female) who participated in a fully randomized double blind crossover study. The PK parameters were derived using WinNonlin. Covariate analysis of PK profiles was performed using NONMEN and statistically compared using a likelihood ratio test on the difference of objective function value (OFV). Statistical significance for covariate analysis was set at P<0.05(ΔOFV=3.84).

Results: No significant difference in PK parameters between male and female subjects was observed with 0.1 and 0.2 mg doses. However, CL and Vd were significantly different between male and female subjects at the 0.4 mg dose. Results from population covariate modeling analysis indicate that a one-compartment PK model with first-order elimination rate offers best fit for describing INSCOP concentration-time profiles. The inclusion of sex as a covariate enhanced the model fitting (ΔOFV=-4.1) owing to the gender-dependent CL and Vd differences after the 0.4 mg dose.

Conclusion: Statistical modeling of scopolamine concentration-time data suggests gender-dependent pharmacokinetics of scopolamine at the high dose level of 0.4 mg. Clearance of the parent compound was significantly faster and the volume of distribution was significantly higher in males than in females, As a result, including gender as a covariate to the pharmacokinetic model of scopolamine offers the best fit for PK modeling of the drug at dose of 0.4 mg or higher.

BACKGROUND

- Space Motion Sickness (SMS) is an age old problem for astronauts on both short and long duration space flights.
- Scopolamine (SCOP) is the most frequently used drug for the treatment of motion sickness (MS) which is currently available in transdermal patch and tablet dosage forms; these formulations of SCOP are ineffective for the treatment of SMS.
- Intranasal dosage forms are noninvasive with rapid absorption and enhanced bioavailability, thus allowing precise and reduced dosing options alongside the suitability for rescue and treatment.
- An intranasal gel dosage formulation of scopolamine (INSCOP) was developed, and bioavailability and pharmacokinetics (PK) were evaluated under approved protocol in IND guidelines.
- With the increase number of female astronauts participating in space missions, it is crucial to characterize gender differences of PK to ensure the safety and efficacy of INSCOP



Scopolamine

Figure 1. Chemical Structure of Scopolamine

OBJECTIVE

In order to elucidate the effect of gender on the PK of Scopolamine, we examined gender differences in PK parameters of INSCOP at three dose levels of 0.1, 0.2 and 0.4 mg.

METHODS

Treatments:

- Twelve healthy human subjects (6 male/6 female) participated in the study.
- A randomized double blind crossover study design was used with a seven-day washout period between treatments.
- 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.
- Blood samples were gently mixed by inversion and centrifuged at 3000 rpm to separate plasma, which was transferred into cryotubes and stored frozen at -40ºC until analysis.

Sample Analysis:

- Separation and quantification of SCOP concentrations in the sample extracts was achieved using a Waters Acquity UPLC system combined with Micromass Quattro Micro API MA/MS detector using an electrospray interface.
- Positive ions were monitored in the Multiple Reaction Monitoring (MRM) mode.
- Chromatographic separation was accomplished with an Agilent Zorbax SB-CN 50 x 2.1 mm, 5 µ, column.
- Mobile phase : 90:10 (v/v), methanol:2 mM ammonium acetate, pH adjusted to 5.0±0.1, with a flow rate of 0.2 mL/min, injection volume of 10 µL, and run time of 4 minutes.

Data Analysis:

- Individual pharmacokinetic analysis was performed using WinNonlin (version 3.3) by 1-compartment model to obtain pharmacokinetic parameters.
- Differences of individual pharmacokinetic parameters between male and female were tested using student T-test. A customary levels of significance of α=0.05 for significance testing was used.
- Population pharmacokinetic analysis was performed by NONMEN (version7.0).
- Sex, body weight, age were employed as covariates in the model selection.
- Model selection was based on goodness-of-fit in addition to criteria(OFV) of statistical significance.
- Statistical significance for base model building and individual covariate analysis was set at P<0.05{Δ(OFV)=3.84}.

RESULTS

Table 1 Demographics of 12 Subjects

Gender	Male	Female
Age (Mean ± SD)	37 ± 8.5	29 ± 5.4
Body weight (Mean ± SD)	88.7 ± 9.6	72.8 ± 14.3
Average BMI	26	

- After the forward stepwise selection and backward elimination steps, sex was selected to add to the final model which had significant influence on clearance and the volume of distribution of INSCOP.

Table 2 Prediction of PK Parameters from Base Model and Gender Covariate Model

Parameters (Mean±SE)	Population Pharmacokinetics Dose=0.4 mg Unit	Base model	Covariate model	Individual Estimation Male	Female	P value
N		12	6 Male/6 Female	6	6	
OFV		1297.8	1293.7			<0.05 (ΔOFV>3.84)
AIC		1315.8	1307.8			
tvKa	/hr	1.0±0.03	0.97±0.03	2.09±1.75	0.99±0.68	0.18
tvV	L/kg	4.6±0.59	6.8±1.0	14.77±7.33	6.72±3.03	0.03
tvCl	L/(hr*kg)	4.7±0.57	5.3±0.7	6.78±1.68	4.29±1.68	0.03
dCldSEX1		NA	-0.26			
dVdSEX1		NA	-0.52			

Fig. 2 Goodness of Fit Plot of Base Model(DV – Observed concentration, PRED-Population Predicted concentration)

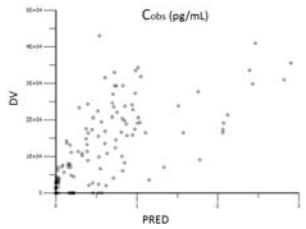


Fig. 3 Goodness of Fit Plot after Covariate Modeling (DV – Observed concentration, PRED-Population Predicted concentration)

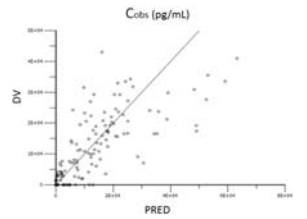


Fig. 4 Weighted Residuals versus Population Prediction Profile for Base Model

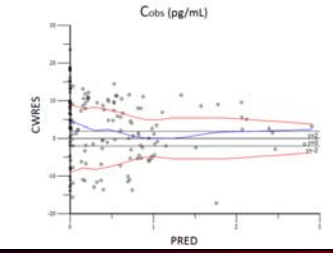
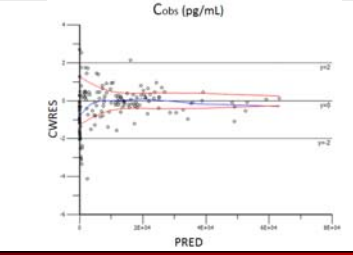


Fig. 5 Weighted Residuals versus Population Prediction Profile for Gender Covariate Model



CONCLUSIONS

- We determined the population pharmacokinetic model for INSCOP and established the gender-dependent pharmacokinetics of scopolamine.
- Clearance of the parent compound was significantly faster and the volume of distribution was significantly higher in males than in females, As a result, including gender as a covariate to the pharmacokinetic model of scopolamine offers the best fit for PK modeling of the drug at dose of 0.4 mg or higher.