Pharmacokinetics of intranasal scopolamine gel formulation during antiothostatic bed rest, a microgravity analog
Rajendra P. Singh¹, Vernie R. Daniels², Camille J. Crady², H. Derendorf³ and L. Putcha³
¹Department of Pharmacoeconomics, University of Florida, Gainesville, FL; ²Wyle Integrated Science & Engineering, Houston, TX; ³NASA Johnson Space Center, Houston, TX

INTRODUCTION

Motion sickness (MS) is a long-standing problem for space travelers on short and long duration space flights. Oral antiemetics are not very effective in space due to poor bioavailability. Scopolamine (SCOP) is the most frequently used drug for the treatment of motion sickness, and is available as 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 in addition to offering rescue and treatment options. An intranasal gel dosage formulation of scopolamine (INSCOP) was developed and pharmacokinetics (PK) and bioavailability were determined in clinical trials with human subjects under IN guidelines.

Description of Methods and Materials: The present clinical trial compares PK and bioavailability of INSCOP in 12 normal, healthy subjects (6 male & 6 female) during ambulation (AMB) and antiothostatic bed rest (ABR) used as a ground-based microgravity analog. Subjects received 0.2 mg and 0.4 mg doses of INSCOP during AMB and ABR in a 4-way crossover design.

Data and Results: Results indicated no difference between AMB and ABR in PK parameters after 0.2 mg dose. Clearance (Cis) decreased with a concomitant increase in maximum concentration and area under concentration-versus-time curve (AUC) during ABR after the 0.4 mg dose.

Interpretation, Conclusion or Significance: The difference in AUC and Cis at the higher (0.4 mg) but not the lower dose (0.2 mg) during ABR suggests that ABR may affect metabolism and/or clearance of INSCOP at higher doses. These results indicate that dosing adjustment may be required for treatment of SMS with INSCOP in space.

METHODS

Scopolamine (SCOP) is frequently used for the treatment of motion sickness (MS), and is available as 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 in addition to offering rescue and treatment options. An intranasal gel dosage formulation of scopolamine (INSCOP) was developed and pharmacokinetics (PK) and bioavailability were determined in clinical trials with human subjects under IN guidelines.

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RESULTS

The plasma concentration time profiles were analyzed using the non-compartmental method. After administration of the 0.2 mg dose of INSCOP during AMB and ABR, AUC values were similar with no significant difference at 95% CI. However, AUC values were significantly different after 0.4 mg dose. All relevant PK parameter estimates are listed in Table 1.

The parameters were evaluated for bioequivalence between AMB and ABR. Results of this evaluation (table 2) showed that the two doses are not bioequivalent with ratios at 90% CI, and are outside the specified limits of 80 and 125%.

CONCLUSIONS

After intranasal administration of scopolamine to human subjects during AMB and ABR conditions PK parameters were similar at the low dose (0.2 mg), but not at the high dose (0.4 mg) between the two conditions. Comparison of Cmax and AUC values suggest that treatments between the two conditions were not bioequivalent when the 90% confidence intervals fell outside the specified limits of 80 and 125% for both doses tested.

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