Effects of pH and Dose on Nasal Absorption of Scopolamine Hydrobromide in Human Subjects

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Purpose. The present study was conducted to evaluate the effects of formulation pH and dose on nasal absorption of scopolamine hydrobromide, the single most effective drug available for the prevention of nausea and vomiting induced by motion sickness.

Methods. Human subjects received scopolamine nasally at a dose of 0.2 mg/0.05 mL or 0.4 mg/0.10 mL, blood samples were collected at different time points, and plasma scopolamine concentrations were determined by LC-MS/MS.

Results. Following administration of a 0.2 mg dose, the average C_{max} values were found to be 262 ± 118, 419 ± 161, and 488 ± 331 pg/mL for pH 4.0, 7.0, and 9.0 formulations, respectively. At the 0.4 mg dose the average C_{max} values were found to be 503 ± 199, 933 ± 449, and 1,308 ± 473 pg/mL for pH 4.0, 7.0, and 9.0 formulations, respectively. At a 0.2 mg dose, the AUC values were found to be 23,208 ± 6,824, 29,145 ± 9,225, and 25,721 ± 5,294 pg.min/mL for formulation pH 4.0, 7.0, and 9.0, respectively. At a 0.4 mg dose, the average AUC value was found to be high for pH 9.0 formulation (70,740 ± 29,381 pg.min/mL) as compared to those of pH 4.0 (59,573 ± 13,700 pg.min/mL) and pH 7.0 (55,298 ± 17,305 pg.min/mL) formulations. Both the C_{max} and AUC values were almost doubled with doubling the dose. On the other hand, the average T_{max} values decreased linearly with a decrease in formulation pH at both doses. For example, at a 0.4 mg dose, the average T_{max} values were 26.7 ± 5.8, 15.0 ± 10.0, and 8.8 ± 2.5 minutes at formulation pH 4.0, 7.0, and 9.0, respectively.

Conclusions. Nasal absorption of scopolamine hydrobromide in human subjects increased substantially with increases in formulation pH and dose.

KEY WORDS: scopolamine; motion sickness; nasal absorption; pH effect; dose effect.

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INTRODUCTION

Scopolamine is a naturally occurring antimuscarinic agent. It is one of the principal antimuscarinic components of the belladonna alkaloids. Scopolamine has been used therapeutically for almost 200 years and generally exhibits the pharmacological actions associated with other antimuscarinic agents. Although other antimuscarinic agents have been used in the prevention of nausea and vomiting induced by motion sickness, it appears that scopolamine is most effective (1–4). However, this drug has a very low and variable oral bioavailability because of extensive hepatic first-pass metabolism (5). The variability in absorption and poor bioavailability of oral administration of scopolamine indicate that this route is neither reliable nor effective for this drug. The transdermal administration of scopolamine also has limitations. For example, the peak plasma concentration (C_{max}) is not reached until 12–16 h after dosing (6,7). Moreover, this route provides unnecessary prolonged blood levels that result in a significant side effect profile which includes dry mouth, drowsiness and blurred vision (7).

Nasal administration has gained tremendous attention by many researchers within the last few decades due to its great potential utility for rapid drug delivery. It offers an attractive alternative for drugs that have limited oral bioavailability, are destroyed by gastrointestinal fluids, or are highly susceptible to hepatic first-pass or gut-wall metabolism (8). Nasal drug delivery also offers the convenience and safety of being noninvasive. In addition, nasal drug administration results in quick onset of action as compared to oral, sublingual and transdermal administrations. It has been reported, nearly 50 years ago, that nasal scopolamine could produce a faster response, greater therapeutic activity, and more complete absorption than an equivalent oral dose (9,10).

Although there are published reports on the nasal administration of scopolamine, the effects of formulation variables on nasal absorption are not comprehensively covered. The purpose of this study was to evaluate the effects of formulation pH and dose on nasal absorption of scopolamine hydrobromide in human subjects.

MATERIALS AND METHODS

Materials

Scopolamine hydrobromide was obtained from Boehringer Ingelheim (Petersburg, VA, USA). Citric acid, dibasic sodium phosphate and sodium chloride were purchased from Amresco (Solon, OH, USA). Benzalkonium chloride was obtained from Stepan (Elwood, IL, USA). Sodium chloride and hydrochloric acid were purchased from Spectrum (Gardena, CA, USA). Other reagents were of analytical grade. Purified water of USP grade was used for formulation preparation.

Subjects

Eighteen healthy male subjects between the ages of 18 and 45 years participated in this study. The subjects were judged to be healthy and of normal body weight from results of prestudy physical examination, blood chemistry, and electrocardiographic evaluations. The study was conducted at State University of New York Medical Center, Stony Brook, NY, under a

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university IRB approved study protocol. Written consent was obtained from each subject. The research followed the tenets of the Declaration of Helsinki promulgated in 1964.

Protocol

The subjects were given breakfast 1h before drug administration and were restricted from eating and drinking during the study. Formulations of pH 4.0, 7.0 and 9.0 were used. The formulations were administered into nostril as spray with a nasal actuator. The dose was either 0.2 mg/0.05 mL or 0.4 mg/0.10 mL of scopolamine hydrobromide.

Blood samples (~7 mL) were obtained via an indwelling catheter placed in each subject's antecubital vein. Samples were collected into vacutainers containing sodium heparin as anticoagulant before the drug was administered and at 5, 10, 15, 20, 25, 30, 45, 60, 120, and 240 minutes after administration. Blood samples were centrifuged and the plasma was collected and frozen at −20°C until analysis.

Side effect profile which includes nasal itching, nasal burning, unusual taste, emesis, dry mouth, nausea, headache, drowsiness, dizziness, and blurred vision, was monitored during the study period.

Preparation of Formulations

Three batches of scopolamine hydrobromide solutions of 4 mg/g drug concentration were prepared at pH 4.0, 7.0 and 9.0. The formulation compositions are given in Table 1.

Bioanalytical Methods

A bioanalytical method for the determination of free scopolamine in human plasma was developed and validated by KeyStone Analytical Laboratories (North Wales, Pennsylvania). Hyoscyamine was used as the internal standard. The assay for free scopolamine in human plasma was performed by extracting scopolamine from alkaline plasma in methyl-t-butyl ether and then analyzing the extract by LC-MS/MS method. This procedure was found to be satisfactory for the determination of free scopolamine in human plasma over the concentration range of 20–50 pg/mL. The limit of quantitation of this assay was established at 20 pg/mL.

Data Analysis

The areas under the drug concentration vs time curves (AUC) were calculated for from the linear trapezoidal method (11). Values of maximum concentration (C_{max}) and time of maximum concentration (T_{max}) were determined by inspection from the plasma concentration-time curves. Values were expressed as mean ± standard deviation (SD). The student's *t* test or Mann-Whitney rank sum test was applied, where necessary, to evaluate significance of difference.

RESULTS AND DISCUSSION

In this study, we tested three formulations at two different doses to evaluate the effects of pH and dose on nasal absorption of scopolamine hydrobromide.

Formulations

The compositions of three solution formulations of scopolamine hydrobromide prepared at pHs 4.0, 7.0, and 9.0 for intranasal delivery are presented in Table 1. Scopolamine hydrobromide is the active agent used at 0.4% concentration in all the formulations. Citric acid and dibasic sodium phosphate of different concentrations were used as the buffering agent, to adjust and maintain pH. Sodium chloride was used in different concentrations in various formulations to maintain the isotonicity of final formulations. Benzalkonium chloride was used at 0.02% as antimicrobial agent. Purified water was used as formulation vehicle. Hydrochloric acid and sodium hydroxide were used to adjust pH of the formulations. All of the formulation excipients are of USP or NF grade and are widely used in nasal solution formulation.

Effects of pH on Nasal Absorption

Scopolamine plasma concentrations were increased dramatically with an increase in pH of the dosing solution at both the administered doses (Fig. 1). This indicates that better bioavailability of scopolamine can be achieved by increasing the pH of nasal formulations. The results on the effects of pH on scopolamine absorption are summarized in Table 2. The average C_{max} values following administration of a 0.2 mg dose of scopolamine at pH 4.0 was 262 ± 118 pg/mL. Increasing the pH of the dosing solution to pH 7.0 and 9.0 resulted in higher plasma concentrations of scopolamine which were 419 ± 161 and 488 ± 331 pg/mL, respectively. A similar effect of pH on peak plasma levels was observed following administration of a 0.4 mg dose of scopolamine (The average C_{max} values were 503 ± 199, 933 ± 449 and 1,308 ± 473 pg/mL for pH 4.0, 7.0 and 9.0 formulations, respectively). At a

Table 1. Compositions of Scopolamine Hydrobromide Nasal Solution Formulations

	Quantity/100 mL (g)		
Active agent/excipients	pH 4.0 formulation	pH 7.0 formulation	pH 9.0 formulation
Scopolamine hydrobromide, USP	0.40	0.40	0.40
Citric acid, anhydrous, USP	0.65	0.20	0.04
Dibasic sodium phosphate, USP	0.67	1.44	1.71
Sodium chloride, USP	0.49	0.26	0.20
Benzalkonium chloride(50%), NF	0.04	0.04	0.04
Purified water, USP	100.0 qs	100.0 qs	100.0 qs
Sodium hydroxide, NF Hydrochloric acid, NF		to adjust pH	

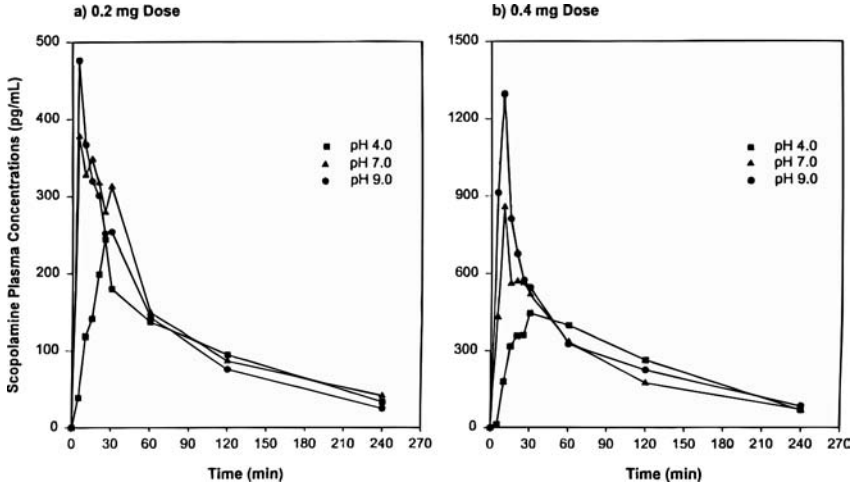

Fig. 1. Effects of formulation pH (4.0, 7.0, and 9.0) and doses (0.2 mg and 0.4 mg) on scopolamine plasma concentration after nasal administration of scopolamine hydrobromide formulations to human subjects.

0.2 mg dose, the AUC value was 23,208 ± 6,824 pg.min/mL at pH 4.0 and was increased to 29,145 ± 9,225 pg.min/mL when pH was increased to 7.0; further increasing pH to 9.0 had no additional effect on the AUC value (25,721 ± 5,294 pg.min/mL). In contrast, at the 0.4 mg dose the AUC values were comparable for both pH 4.0 (59,573 ± 13,700 pg.min/mL) and pH 7.0 (55,298 ± 17,305 pg.min/mL) formulations; however, the value was higher at pH 9.0 (70,740 ± 29,381 pg.min/mL). The average T_{max} values decreased with an increase in formulation pH, 22.5 ± 4.18 and 26.7 ± 8.80 minutes for pH 4.0 formulation at 0.2 and 0.4 mg doses, respectively; 10.0 ± 5.80 and 15.0 ± 10.0 minutes for pH 7.0 formulation at 0.2 and 0.4 mg doses, respectively; and 6.20 ± 2.50 and 8.80 ± 2.50 minutes for pH 9.0 formulation at 0.2 and 0.4 mg doses, respectively. This suggests that the absorption rate of scopolamine is more rapid under basic than acidic conditions. This may be a function of the dissolution characteristics of the weakly basic tertiary amine, scopolamine.

Nasal absorption of drug is generally pH dependent. Several studies have been reported by other investigators on the effects of pH on nasal absorption of drugs but, in most cases animals were used instead of human subjects (12–17). Protein or peptide-based drugs were mainly used in these studies and in contrast to our findings on scopolamine, they found higher nasal absorption at a lower pH. For example, Nomura et al. reported that intranasal absorption of E.coli-rhG-CSF in rats

Table 2. Summary of Scopolamine Plasma Concentrations, C_{max}, T_{max}, and AUC in Healthy Human Volunteers (n = 18) After 0.2 or 0.4 mg Intranasal Administration of Scopolamine Hydrobromide from Formulations of Different pHs

Time (minutes)	Plasma concentration of scopolamine free base (pg/mL) (Ave ± SD)					
	pH 4.0 formulation		pH 7.0 formulation		pH 9.0 formulation	
	0.2 mg dose	0.4 mg dose	0.2 mg dose	0.4 mg dose	0.2 mg dose	0.4 mg dose
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
5	38.5 ± 43.2	12.3 ± 21.4	378 ± 160	431 ± 321	476 ± 434	913 ± 378
10	118 ± 55.5	179 ± 147	328 ± 162	856 ± 538	367 ± 143	1,296 ± 493
15	141 ± 49.3	316 ± 264	348 ± 169	561 ± 240	320 ± 131	810 ± 495
20	199 ± 112	357 ± 281	318 ± 183	570 ± 257	301 ± 70.6	676 ± 296
25	243 ± 123	361 ± 110	279 ± 116	563 ± 185	251 ± 48.8	574 ± 290
30	180 ± 95.3	446 ± 140	313 ± 124	519 ± 105	253 ± 44.8	546 ± 286
60	137 ± 55.0	399 ± 115	149 ± 84.9	334 ± 58.5	143 ± 16.2	326 ± 175
120	95 ± 24.1	264 ± 33.5	86.5 ± 4.80	173 ± 18.1	75.8 ± 14.5	224 ± 97.1
240	33.0 ± 7.80	66.3 ± 40.7	40.5 ± 3.70	68.7 ± 5.50	24.3 ± 11.1	81.8 ± 34.6
C_{max} (pg/mL)	262 ± 118	503 ± 199*	419 ± 161**	933 ± 449*,**	488 ± 331**	1,308 ± 473*,**
T_{max} (min)	22.5 ± 4.18	26.7 ± 5.77	10.0 ± 5.80***	15.0 ± 10.0***	6.25 ± 2.50***	8.80 ± 2.50***
AUC (pg.min/mL)	23,208 ± 6,824	59,573 ± 13,700****	29,145 ± 9,225	55,298 ± 17,305****	25,721 ± 5,294	70,740 ± 29,381****

*$p < 0.05$ compared with C_{max} of corresponding 0.2 mg dose.
**$p < 0.05$ compared with C_{max} of corresponding dose at pH 4.
***$p < 0.05$ compared with T_{max} of corresponding dose at pH 4.
****$p < 0.05$ compared with AUC of corresponding 0.2 mg dose.

enhanced by a decrease in pH (13) and Ohkawa et al. showed the similar pH effect in rats for secretin (16). Hirai et al. reported maximum nasal absorption of insulin in dogs at a pH 3.1 and the absorption gradually decreased with the increase in pH till pH 6.1. However, after the pH was increased to greater than 6.1, there was an increase in nasal absorption of insulin with an increase in pH (17).

Effects of Dose on Nasal Absorption

The effects of doses, 0.2 mg and 0.4 mg, on human nasal absorption of scopolamine from different pH formulations, 4.0, 7.0, and, 9.0, are also depicted in Fig. 1 and Table 2. The C_{max} and AUC values were almost doubled when the dose of scopolamine was increased two fold; however, the T_{max} values were found to be higher at the 0.4 mg dose. Our findings on the effects of dose on nasal absorption of scopolamine are in good agreement with many previous reports on other drugs (13,15,16).

Side Effects

Side effects including nasal itching, nasal burning, unusual taste, emesis, dry mouth, nausea, headache, drowsiness, dizziness, and blurred vision, were monitored during the study period. Although C_{max} was found to be as high as 1,307 $\pm$ 473 pg/mL after administration of a 0.4 mg dose of pH 9.0 formulation, no significant adverse effect was observed with any of the formulations during the study period.

Overall it can be concluded that the formulation pH has significant effects on nasal absorption of scopolamine and the absorption can be enhanced dramatically with an increase in formulation pH. In addition, increase of dose can also enhance nasal absorption proportionally. These findings can be used for the development of optimal formulations of scopolamine hydrobromide.

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