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Report

Pharmacokinetics and Oral Bioavailability of Scopolamine in Normal Subjects

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The pharmacokinetics and bioavailability of scopolamine were evaluated in six healthy male subjects receiving 0.4 mg of the drug by either oral or intravenous administration. Plasma and urine samples were analyzed using a radioreceptor binding assay. After iv administration, scopolamine concentrations in the plasma declined in a biexponential fashion, with a rapid distribution phase and a comparatively slow elimination phase. Mean and SE values for volume of distribution, systemic clearance, and renal clearance were 1.4 ± 0.3 liters/kg, 65.3 ± 5.2 liters/hr, and 4.2 ± 1.4 liters/hr, respectively. Mean peak plasma concentrations were 2909.8 ± 240.9 pg/ml following iv administration and 528.6 ± 109.4 pg/ml following oral administration. Elimination half-life of the drug was 4.5 ± 1.7 hr. Bioavailability of the oral dose was variable among subjects, ranging between 10.7 and 48.2%. The variability in absorption and poor bioavailability of oral scopolamine indicate that this route of administration may not be reliable and effective.

KEY WORDS: pharmacokinetics; scopolamine; drug disposition; motion sickness drug.

INTRODUCTION

Scopolamine is an anticholinergic, antiemetic agent with a wide range of clinical applications resulting from its diverse pharmacologic activity. Several reports on the pharmacology and biochemistry of the drug are available (1,2), but relatively little is known about the pharmacokinetics and bioavailability of scopolamine. Earlier pharmacokinetic evaluations of the drug were based on urinary excretion (3), which accounted for less than 5% of the administered dose. Chandrasekaran *et al.* reported that blood concentration–time data following oral scopolamine administration to one subject did not provide adequate pharmacokinetic information (4). The results of a recent study on the pharmacokinetics of scopolamine in patients anesthetized for cesarean section indicated that the serum levels were measurable up to only 3 hr after dosing when administered by intravenous, intramuscular, or oropharyngeal routes (5). After the development in our laboratory of a sensitive and specific analytical procedure for the determination of scopolamine concentrations (6), the current investigation was conducted to characterize the pharmacokinetics and bioavailability of the drug following iv and oral administration to human subjects.

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METHODS

Subjects. Six healthy, nonsmoking male volunteers between 25 and 45 years of age participated in the study. The study protocol was approved by the Human Research Policy and Procedures Committee at the NASA/Johnson Space Center. Informed written consent was obtained from each subject during the prestudy briefing session.

Study Design. After an overnight (>10-hr) fast, each subject received 0.4 mg of scopolamine as scopolamine hydrobromide by either intravenous injection (Burroughs Wellcome, Chapel Hill, N.C.) or oral administration of a tablet. The tablets were custom manufactured for use in this study by A. C. Ingle & Co., Houston, Texas. The content variability of scopolamine for the tablets was less than 10% and the tablet weight uniformity was 95%. Tablets disintegrated immediately after placing them in 30 ml of deionized water. The dissolution rate of the tablets was rapid, with more than 95% of the drug dissolving in less than 10 min. Blood samples were collected once before the drug was administered and at 0.16, 0.33, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hr after administration. The samples were centrifuged, and plasma was collected and stored frozen at −20°C. Total urine voids were collected at regular time intervals for 24 hr after drug administration. Urine voids were recorded, and aliquots of all samples were stored frozen at −20°C.

Sample Analysis. Plasma and urine samples were analyzed using a combined reverse-phase liquid chromatographic–radioreceptor binding assay (6). The analysis con-

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sisted of two phases. In the first phase, Sep-Pak C18 cartridges (Waters Associates) were used to remove interfering compounds from the biological samples. In the second phase, quantitative determinations of scopolamine concentrations were accomplished using competitive radioreceptor binding to calf brain muscarinic receptors. Tritiated methyl scopolamine (Sigma; sp act, 53.5 μCi/mmol) was used as a tracer, and scopolamine hydrobromide was used for the assay standards. The overall recovery of scopolamine was >85%, with a coefficient of variation of <12% between assays. The sensitivity limit for scopolamine base was 25 pg/ml in plasma and 50 pg/ml in urine.

Pharmacokinetic Analysis. Semilogarithmic plots of plasma scopolamine concentration versus time following intravenous or oral administration exhibited biphasic disposition. Equations (1) and (2) were fit to the intravenous and oral data sets, respectively, using nonlinear least-squares regression (7):

$$C = Ae^{\alpha t} + Be^{-\beta t} \quad (1)$$

$$C = A'e^{-\alpha t} + B'e^{\beta t} - (A' + B')e^{-k_a t} \quad (2)$$

where C represents the plasma concentration, t is the time, k_a, α, and β are the first-order rate constants for absorption, distribution, and elimination, and A, B, A', and B' are the respective coefficients. Initial estimates were obtained by computerized curve stripping (8), and the data were weighted by the factor $1/C^2$. From the final estimates of the parameters of Eqs. (1) and (2), other relevant pharmacokinetic parameters such as total clearance (CL), renal clearance (CL_r), volume of distribution (V), half-life ($t_{1/2}$), area under the drug concentration in plasma versus time curve for the intravenous (AUC_{iv}) and oral (AUC_{po}) treatments, and absolute bioavailability of scopolamine after oral administration (F) were calculated using standard equations (9). The urinary excretion rate data obtained after iv administration were fit simultaneously with the plasma concentration–time data according to the equation $1 \times CL_r$. Where appropriate, comparisons of parameters between sample sets and treatments were made using a paired t test.

RESULTS

Mean plasma concentration–time profiles following intravenous and oral administration of a 0.4-mg dose of scopolamine to normal subjects are presented in Fig. 1. Plasma concentration–time profiles of scopolamine appeared to decline in a biexponential manner, with a rapid distribution phase and a comparatively slow elimination phase. Urinary excretion rate profiles of scopolamine following iv and oral administration are presented in Fig. 2 and are in close agreement with the respective plasma concentration profiles.

Pharmacokinetic parameters of scopolamine after iv administration are presented in Table I. Scopolamine appears to be well distributed out of the plasma, with a volume of distribution of 1.36 ± 0.28 liters/kg. It was rapidly eliminated from the body, with a total-body clearance of 65.2 ± 5.2 liters/hr. Renal clearance of the unmetabolized drug was only 4.2 ± 1.3 liters/hr.

Scopolamine parameters obtained after oral administration are presented in Table II. The data in this table indicate that the drug was absorbed rapidly from the gastrointestinal

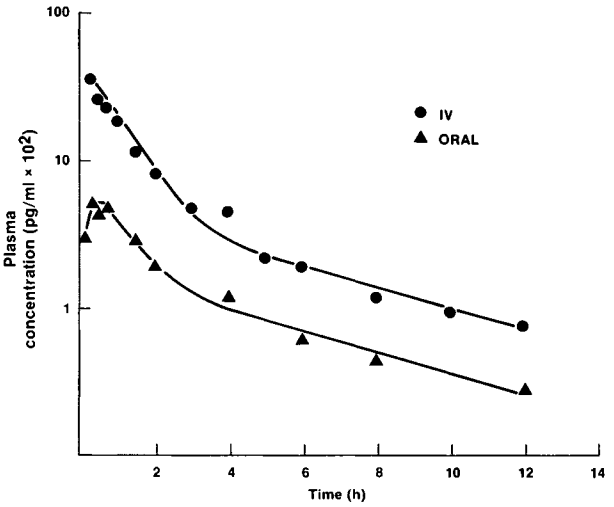

Fig. 1. Plasma concentration versus time profiles of scopolamine following intravenous and oral administration of a 0.4-mg dose to a subject.

tract, reaching peak plasma concentrations less than 1 hr (0.78 ±0.30 hr) after administration. Peak plasma concentrations were variable with a mean concentration of 528.6 pg/ml. After oral administration, the rate of absorption and half-life of the drug were also variable and ranged between 0.8 and 6.3 hr^{-1} and 1.4 and 10.8 hr, respectively. Table III shows the percentage of the dose recovered as scopolamine in the urine over the 24-hr period after administration. Approximately 6% of the iv dose and 1% of the oral dose were eliminated unchanged in the urine. The AUCs and bioavailability estimates calculated from plasma concentration and

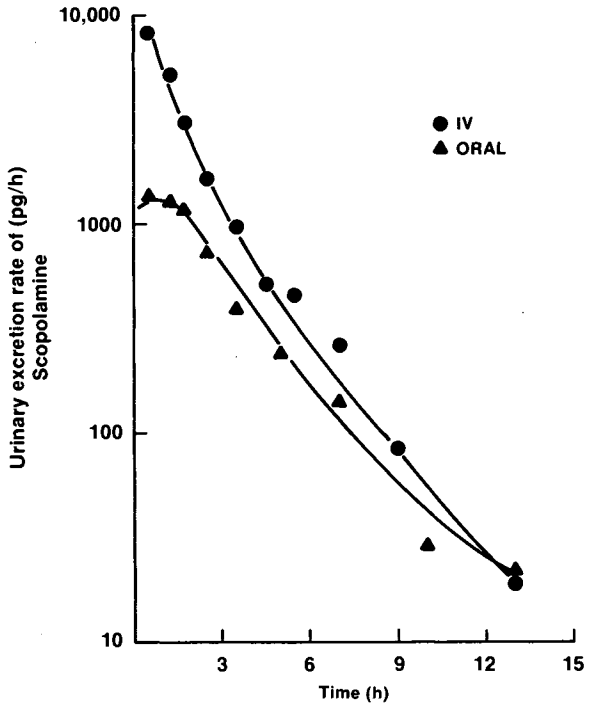

Fig. 2. Urinary excretion rate versus time profiles of scopolamine following intravenous and oral administration of a 0.4-mg dose to a subject.

Table I. Pharmacokinetic Parameters of Scopolamine Following Intravenous Administration of a 0.4-mg Dose to Normal Subjects

Subject No.	Half-life (hr)	Volume of distribution (L/kg)	Clearance (L/hr)	
			Systemic	Renal
1	12.50	0.05	43.66	0.72
2	1.58	1.72	66.16	5.95
3	2.74	1.93	67.01	1.78
4	4.60	1.27	59.76	2.52
5	2.05	1.60	78.86	4.62
6	3.49	1.62	76.02	9.40
Mean	4.49	1.36	65.25	4.17
	(1.66)[a]	(0.28)	(5.17)	(1.30)

[a] Numbers in parentheses are standard errors of the mean.

urinary excretion rate data are presented in Table IV. The estimates obtained from the two methods are in close agreement; the percentage bioavailability ranged between 10.7 and 48.0%.

Using the paired *t* test, the pharmacokinetic parameters calculated from simultaneously fitting plasma concentration–time data and urinary excretion rate profiles of scopolamine were compared (Table V) with those of plasma concentration–time data only. There were no significant differences between the parameters calculated by the two methods.

DISCUSSION

Although scopolamine is a veteran drug that has a wide range of clinical applications, the present investigation constitutes the first comprehensive evaluation of its pharmacokinetics and bioavailability. Inadequate and cumbersome analytical procedures for determining therapeutic concentrations of the drug limited the understanding of the pharmacokinetic behavior and metabolism of scopolamine in humans and in animal models. The combined reverse-phase liquid chromatographic-radioreceptor binding assay developed in our laboratory for detecting picogram levels of the drug in biological fluids makes clinical pharmacokinetic evaluations and therapeutic drug monitoring possible.

Results of the present investigation indicate that after administration, plasma concentration–time profiles of scopolamine exhibit a biexponential decline in the postabsorptive phases. These results are similar to those reported earlier for atropine (10), suggesting a rapid distribution of both drugs. Scopolamine, however, is eliminated from the systemic circulation more slowly than atropine as indicated by the half-lives (2.5 and 4.5 hr, respectively). These results suggest that the pharmacologic effect of scopolamine may persist for a longer duration than that of atropine provided that both drugs have similar pharmacodynamic profiles. No drug could be detected in the plasma or urine after 12 hr, indicating that scopolamine may not have a potential to accumulate in the body. Pharmacokinetic parameters from all the subjects are in close agreement except those from subject No. 1. In this subject, the elimination half-life of scopolamine was 12.5 hr. This long half-life may be a result of poor systemic and renal clearance of the drug. It may also have resulted from insufficient data points during the terminal log-linear phase of the plasma concentration profile from which half-life estimates were derived.

Pihlajamaki *et al.* reported a large intersubject variability in the pharmacokinetic parameters after iv administration of scopolamine to women undergoing cesarean section (5). This intersubject variability makes it difficult to compare the parameters from Pihlajamaki's investigation with those from

Table II. Pharmacokinetic Parameters of Scopolamine Following Oral Administration of 0.4-mg Tablets to Normal Subjects[a]

Subject No.	K_a (hr^{-1})	C_{max} (pg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
1	4.7	427.3	0.75	10.8
2	4.1	531.8	0.50	1.4
3	0.8	249.4	2.00	6.5
4	6.3	517.3	0.33	6.3
5[b]	—	—	—	2.6
6	2.0	917.3	0.33	2.4
Mean	3.58	528.6	0.78	5.0
	(2.2)	(109.4)	(0.3)	(1.4)

[a] Numbers in parentheses are standard errors of the mean. K_a, absorption rate constant; C_{max}, maximum plasma concentration; T_{max}, time to reach maximum concentration; $t_{1/2}$, half-life.
[b] Inadequate samples obtained during absorption phase.

Table III. Recovery (Percentage of Dose) of Scopolamine in the Urine After iv and Oral Administration of 0.4 mg to Normal Subjects

Subject No.	Route of administration	
	iv	Oral
1	1.72	0.53
2	8.99	0.96
3	2.64	0.35
4	4.22	1.21
5	5.91	0.64
6	12.40	2.36
Mean	5.98	1.01
	(1.66)[a]	(0.30)

[a] Numbers in parentheses are standard errors of the mean.

the present study. However, it appears that the clearance of scopolamine in women who have undergone cesarean section is faster than in normal male subjects, resulting in a shorter half-life in the former. This may be an effect of increased basal metabolic rate in pregnant women or a result of experimental differences between the two studies, such as the route and dose of administration and analytical methodology.

Like the other tertiary amines, the rate and extent of absorption of scopolamine exhibit a large intersubject variability as indicated by the wide ranges of C_{max} and T_{max}. Absorption rates (Table II), however, indicate a rapid absorption of the drug from the gastrointestinal tract, with a mean absorption half-life of 11.5 min. Pihlajamaki *et al.* observed analogous results after oropharyngeal administration of the drug (5). Muir and Metcalfe also reported a similar trend in the absorption of scopolamine from an oral dose (415 μg), with peak plasma concentrations of 1.2 nmol/liter (364 pg/ml) reached in 0.5 hr in 5 of the 10 subjects tested and 0.76 nmol/liter (230 pg/ml) reached in 1 hr in the remainder of the subjects (11).

A major clinical effect of anticholinergics such as atropine and scopolamine is suppression of gastric secretions and intestinal motility (12). Both these factors play an important role in the gastrointestinal absorption of drugs and may influence absorption in both scopolamine and atropine. Reports indicate that scopolamine and atropine are comparable in their absorption and distribution characteristics. Kanto *et al.* reported poor (25.6%) and variable oropharyngeal absorption of atropine compared to an equal dose of im or iv administration in women anesthetized for cesarean section (10). In our study, the mean peak plasma concentration after oral administration was less than 10% of the peak concentration after an equal iv dose of scopolamine. Less than desirable absorption of the drug from the gastrointestinal tract is also evident from the urinary excretion data. The mean percentage of the dose recovered as scopolamine in the urine was lower after oral administration than after iv dosing (Table III). This may be a result of either extensive first-pass metabolism or incomplete absorption of scopolamine from the gastrointestinal tract. Predominant nonrenal elimination of scopolamine indicated by the low renal clearance of the parent compound (Table I) supports the possibility that first-pass metabolism may be occurring after oral administration as reported for drugs with a high hepatic extraction ratio (13). The systemic availability of an oral dose of scopolamine calculated using clearance and average hepatic blood flow (9) was 27.5 ± 5.7, which is in close agreement with the observed bioavailability of the drug (Table IV). This agreement strongly suggests the existence of presystemic hepatic metabolism of scopolamine administered orally. Further evidence of incomplete availability of the drug from an oral dose comes from the incidence of side effects after iv and oral administration. Immediately after iv administration, scopolamine produced acute salivary depression and sedation for approximately 1–2 hr and blurred vision for about 0.5 hr. These side effects were absent in the subjects after receiving an equivalent oral dose.

Scopolamine is an alkaloid with a pK_a of 8.2, which falls in the critical range of pH-dependent excretion for weak bases (14). This suggests that urinary excretion of the drug may be dependent on urinary pH. However, since the contribution of renal clearance to the total clearance of the drug is small (<2%), the susceptibility to pH-dependent changes in the urinary excretion may not significantly influence the elimination of scopolamine. Comparison of pharmacokinetic parameters and bioavailability estimates derived from plasma concentration–time data and urinary excretion rate

Table IV. Bioavailability (Percentage) of Scopolamine Following Oral Administration of 0.4-mg Tablets to Normal Subjects

Subject No.	AUC_{iv}[a] (pg · hr/ml)	AUC_{po}[a] (pg · hr/ml)	Bioavailability (%)	
			Plasma	Urine
1	9162	4413	48.2	30.9
2	6046	1859	30.7	10.7
3	5969	698	11.7	13.3
4	6693	1705	25.5	28.7
5	5073	1362	26.8	10.8
6	5262	945	18.0	19.0
Mean	6368	2358	26.8	18.9
	(608)[b]	(764)	(5.1)	(3.6)

[a] Area under the drug concentration in plasma versus time curve.
[b] Numbers in parentheses are standard errors of the mean.

Table V. Comparison of Pharmacokinetic Parameters Derived by Simultaneous Fitting of Plasma Concentration and Urinary Excretion Rate–Time Data and Plasma Concentration–Time Data Only[a]

Data	$t_{1/2}$ (hr)	V (L/hr)	CL_s (L/hr)	CL_r (L/hr)	AUC (pg · hr/ml)
Plasma concentration–time	4.49	1.36	65.25	4.17	6368
	(1.66)	(0.28)	(5.17)	(1.30)	(608)
Plasma concentration and urinary excretion rate–time	4.19	1.58	66.4	1.38	5557
	(1.4)	(0.57)	(12.6)	(1.37)	(545)

[a] $t_{1/2}$, half-life; V, volume of distribution; CL_s, systemic clearance; CL_r, renal clearance; AUC, area under the drug concentration in plasma versus time curve. Numbers in parentheses are standard errors of the mean. Paired t test indicated no significant differences between the two estimates ($P < 0.05$) for any of the parameters.

data suggests, although only a small portion of the administered dose is eliminated in the urine as scopolamine, urinary excretion rate data can yield valuable information about the pharmacokinetics and bioavailability of the drug. Less than 5–8% of the administered dose is eliminated unchanged in the urine. This is in agreement with earlier reports of 4–5% excretion (3).

In conclusion, results of this study indicate that scopolamine administered as an oral dose is absorbed rapidly from the gastrointestinal tract and has a poor bioavailability. This low bioavailability may be a result of a significant enterohepatic metabolism of the drug before absorption from the gastrointestinal tract. Scopolamine is rapidly eliminated from the systemic circulation, with an average half-life of 4.5 hr. Less than 2% of the total clearance is by renal elimination of unchanged drug, indicating that hepatic metabolism may be the primary route of disposition. Further evaluation of urinary excretion of scopolamine and its metabolites after iv and oral administration may be helpful in assessing the factors affecting the bioavailability of the drug. The pharmacologic effect and therapeutic benefit of oral scopolamine should be carefully examined because of the variable and incomplete absorption from the gastrointestinal tract. It may be beneficial to evaluate alternate routes of administration (e.g., buccal and sublingual) of scopolamine to assess therapeutic reliability and pharmacologic effectiveness.

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