

ADME NTP Study S0264 Scopolamine hydrobromide Toxicokinetics

Sex/Species: male and female F344 rats, male and female B6C3F1 mice.

Vehicle: intravenous, water; oral, water.

CASRN 114-49-8

Radiolabeled with tritium in the amine moiety; [N-methyl ³H]-Scopolamine hydrobromide

Studies Performed:

- Single 5 mg/kg intravenous dose to male rats with blood sampling at 10, 20, 30, 40, 50, 60, 120, 240, and 360 minutes postdose. (n = 3 per time point; total of 9 animals sampled on a rotating basis)
- Single 5 mg/kg oral gavage dose to male and female rats with blood sampling at 30, 60, 120, 360, 720, and 1440 minutes postdose. (n = 3 per time point)
- Single 25 mg/kg oral gavage dose to male rats with blood sampling at 15, 30, 60, 120, 240, 360, and 1440 minutes postdose. (n = 3)
- Single 25 mg/kg oral gavage dose to male rats with sacrifice at 15 (n = 1), 30 (n = 1), or 1440 (n = 3) minutes postdose.
- Single 5 mg/kg oral gavage dose to male and female mice with blood sampling at 15, 30, 60, 120, and 360 minutes postdose. (n = 3 per time point)
- Single 25 mg/kg oral gavage dose to male and female mice with blood sampling at 15, 30, 60, 120, 240, and 360 minutes postdose. (n = 3 per time point)

For data of mean and standard deviation of triplicate determinations, plasma samples from three animals were pooled and the pooled samples analyzed in triplicate.

Toxicokinetics:

Plasma samples from three male rats at each time point were pooled following a single 5 mg/kg bodyweight intravenous dose of [³H]Scopolamine hydrobromide. The pooled samples were extracted and analyzed by radio-TLC and reported as the total and base-extractable radioactivity for each time point. Each pooled sample was analyzed in triplicate (Table 1).

The toxicokinetic parameters for the mean plasma concentration-time profile for the pooled plasma samples from intravenously dosed rats are presented in Table 2. The profile for scopolamine concentration appeared to decline in a biexponential manner with a rapid distribution phase and a comparatively slower elimination phase. The data were best fit to a two compartment model (coefficient of correlation 0.993).

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TABLE 1

Mean Total and Base-Extractable Radioactivity in the Estimated Total Plasma Volume and Plasma Scopolamine Concentration Following Administration of a Single Intravenous Dose of ³H-Scopolamine-HBr to Male Fischer 344 Rats at 5 mg/kg.

Time (Min)	Total Radioactivity (% of Dose)	Extractable Radioactivity (% of Dose)	Scopolamine (ng/ml)
10	1.84 ± 0.21	0.78 ± 0.04	1126
20	1.53 ± 0.16	0.52 ± 0.09	750
30	1.25 ± 0.10	0.31 ± 0.03	454
40	1.32 ± 0.13	0.30 ± 0.05	428
50	1.23 ± 0.04	0.24 ± 0.01	336
60	1.05 ± 0.03	0.14 ± <0.01	197
120	0.97 ± 0.09	0.07 ± 0.02	102
240	0.87 ± 0.03	0.02 ± <0.01	32
360	0.88 ± 0.07	0.02 ± <0.01	26

**Data presented are the mean and S.D. of triplicate determinations.
Rat total plasma volume was estimated at 3.5 ml/kg.
Specific Activity: 44 dpm/ng Scopolamine**

TABLE 2

Pharmacokinetic Parameters of Scopolamine Following Administration of a Single Intravenous Dose of ³H-Scopolamine-HBr To Fischer 344 Rats at 5 mg/kg

Pharmacokinetic Parameters	
N	3
t_{1/2} α (min)	22.3
t_{1/2} β (min)	255
β (1/min)	0.003
AUC (ng/mlmin)	62480
Coef. of Corr.	0.993
Vd (l/kg)	29.6
CL (l/kg min)	0.08

TABLE 3

Mean Total Radioactivity in the Estimated Blood and Plasma Volumes Determined by Sample Oxidation, Following Administration of a Single Oral Dose of ³H-Scopolamine·HBr (5 mg/kg) to Male and Female Fischer 344 Rats

Time (hr)	Whole Blood Radioactivity (% of Dose)		Plasma Radioactivity (% of Dose)		Plasma/Whole Blood (%)	
	Male	Female	Male	Female	Male	Female
0.5	0.38 ± 0.13	0.73 ± 0.77	0.24 ± 0.06	0.52 ± 0.52	65.5 ± 8.4	76.4 ± 6.8
1	0.24 ± 0.04	0.51 ± 0.39	0.15 ± 0.04	0.35 ± 0.28	59.5 ± 7.8	65.7 ± 8.3
2	0.36 ± 0.09	0.42 ± 0.12	0.24 ± 0.07	0.24 ± 0.07	65.6 ± 3.8	62.7 ± 28.3
6	0.27 ± 0.01	0.33 ± 0.11	0.12 ± 0.01	0.37 ± 0.56	43.6 ± 1.5	57.3 ± 12.8
12	0.14 ± 0.02	0.19 ± 0.03	0.10 ± 0.01	0.13 ± 0.04	70.0 ± 12.0	64.3 ± 12.4
24	0.24 ± 0.03	0.24 ± 0.02	0.15 ± 0.03	0.14 ± 0.02	64.5 ± 6.9	58.1 ± 14.3
\bar{x}					61.6	64.1

Data presented are the mean and S.D. of triplicate determinations.
Rat total plasma volume was estimated at 3.5 ml/kg, and rat haematocrit was estimated at 47%.
Specific Activity: 44 dpm/ng Scopolamine.

TABLE 4

Comparison of Total Radioactivity in Estimated Total Plasma Volume Determined by Sample Oxidation and Direct Liquid Scintillation Counting Following Administration of a Single Oral Dose of ^3H -Scopolamine-HBr (5 mg/kg) to Male and Female Fischer 344 Rats

Time (hr)	Oxidized-LSC/LSC (%)	
	Males	Females
0.5	59.7 ± 3.6	44.8 ± 28.5
1	55.3 ± 2.2	51.9 ± 15.4
2	39.5 ± 2.5	29.7 ± 4.0
6	15.5 ± 0.6	29.3 ± 12.6
12	23.3 ± 3.9	28.3 ± 5.7
24	18.1 ± 2.7	18.9 ± 4.1

Data presented are the mean and S.D. of triplicate determinations.

Rat total plasma volume was estimated at 3.5 ml/kg.

Oxidized-LSC = Oxidized and counted by liquid scintillation

LSC = Direct liquid scintillation counting

TABLE 5

Mean Total and Base-Extractable Radioactivity in the Estimated Total Plasma Volume Following a Single Oral Dose of ³H-Scopolamine·HBr to Male and Female B6C3F1 Mice at 5 mg/kg

Time (min)	Total Radioactivity (% of Dose)		Extractable Radioactivity (% of Dose)		Estimated Scopolamine Concentration (ng/ml)	
	Male	Female	Male	Female	Male	Female
15	0.59 ± 0.17	1.13 ± 0.10	0.06 ± 0.02	0.03	92 ± 28	46
30	0.52 ± 0.12	1.21 ± 0.27	0.03 ± <0.01	0.03	41 ± 5	45
60	0.95 ± 0.32	1.05 ± 0.25	0.02 ± <0.01	0.01	35 ± 15	21
120	0.66 ± 0.08	1.92 ± 0.68	0.01 ± <0.01	0.01	15 ± 10	19
240	0.86 ± 0.07	1.01 ± 0.09	<0.01 ± <0.01	<0.01	11 ± 3	3
360	0.32 ± 0.07	0.64 ± 0.49	<0.01 ± <0.01	<0.01	9 ± <1	4

Data presented are the mean and S.D. of triplicate determinations.
 Mouse total plasma volume was estimated at 3.15 ml/100 g.
 Specific Activity: 371 dpm/ng Scopolamine.

TABLE 6
Mean Total Radioactivity in Estimated Total Plasma Volume Determined and Scopolamine Plasma
Concentration Following a Single Oral Dose of ³H-Scopolamine-HBr (25 mg/kg)
To Male Fischer 344 Rats

Time (Min)	Total Radioactivity (% of Dose)	Radiolabelled Components (as % of total eluted radioactivity)				
		Unknown Peak 1 (2 min)	Unknown Peak 2 (3.5 min)	Unknown Peak 3 (6 min)	Scopoline (10 min)	Scopolamine (14 min)
15	0.23 ± 0.15	1.2*	70*	25*	N.D.	7.5 (210 ng/ml)*
30	0.25 ± 0.19	4.0 ± 1.8	66.3 ± 18.6	15.3 ± 6.0	N.D.	N.D.
60	0.31 ± 0.23	15.9 ± 16.2	74.7 ± 13.7	9.4 ± 2.9	N.D.	N.D.
120	0.25 ± 0.14	9.7 ± 2.5	84.0 ± 1.0	5.3 ± 1.3	N.D.	N.D.
240	0.47 ± 0.14	8.9 ± 0.90	86.3 ± 2.3	4.7 ± 2.5	N.D.	N.D.
360	0.45 ± 0.19	8.4 ± 1.9	84.3 ± 4.7	2.9	3.4**	N.D.
1440 (24 hr)	0.95 ± 0.06	5.4 ± 3.7	91.7 ± 4.0	2.4 ± 0.44	0.57**	N.D.

N = 3

N.D. = Not detected - limit of analysis (2 x background ³H) = 50 ng/ml

* = Mean of 2 animals due to loss of HPLC fractions 1-12 (0-6 min)

• Result of one animal - 2 animals ND

** Average of two animals - 1 animal ND

See Figure 6 for reference to unknown peaks.

TABLE 7

Mean Total and Extractable ³H-Equivalents and Estimated Scopolamine Concentrations in Total Plasma Volume Following A Single Oral Dose of ³H-Scopolamine-HBr (25 mg/kg) to Male and Female B6C3F1 Mice

Time (min)	Total Radioactivity (% of Dose)		Extractable Radioactivity (% of Dose)		Estimated Scopolamine Concentration (ng/ml)	
	Male	Female	Male	Female	Male	Female
15	0.62 ± 0.10	0.44 ± 0.19	0.03	0.01	240	104
30	0.75 ± 0.10	0.77 ± 0.07	0.01	0.02	113	151
60	0.78 ± 0.14	0.63 ± 0.23	0.02	<0.01	136	43
120	0.74 ± 0.28	0.71 ± 0.37	<0.01	0.01	35	84
240	0.83 ± 0.11	0.95 ± 0.54	<0.01	0.02	13	154
360	1.14 ± 0.16	0.82 ± 0.37	<0.01	0.01	49	108

Data are the mean and S.D. of triplicate determinations
 Mouse total plasma volume was estimated at 3.15 ml/100 g
 Specific activity (male mice): 199 dpm/ng scopolamine
 Specific activity (female mice): 100 dpm/ng scopolamine

TABLE 8

Tissue Distribution and Excretion of Dosed Radioactivity in Male Fischer Rats Following Administration of a Single Oral Dose of 3H-Scopolamine-HBr at 25 mg/kg

Sample	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5
	15 min	30 min	24 h	24 h	24 h
Radiolabel Recovered (% Dose)					
Stomach	7.27	8.45	0.07	0.07	0.15
Small Intestine	7.50	3.88	0.23	0.26	0.46
Large Intestine	ND	0.16	0.45	0.38	0.65
Blood	1.75	1.50	1.62	1.56	1.44
Liver	9.29	7.58	2.06	2.74	1.99
Muscle	6.56	5.05	6.75	7.48	6.91
Skin	1.86	1.65	2.41	2.42	1.88
All other tissue	1.21	0.88	0.60	0.71	0.71
Stomach Content	66.19	61.01	0.66	0.78	4.96
Small Intestine Content	15.56	8.27	0.96	0.84	2.56
Large Intestine Content	0.22	0.17	36.47	31.82	43.28
Feces	ND	ND	21.52	11.08	0.68
Urine	1.50	3.04	21.70	18.24	17.25
Total Recovered	117.75	97.17	96.21	79.91	84.82

ND = Not detected