Urinary Excretion of Chlorpheniramine and Its Metabolites in Children

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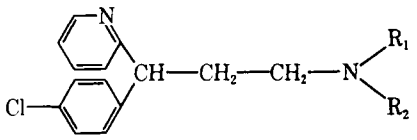
Abstract □ The pharmacokinetics and urinary excretion of chlorpheniramine were studied in 11 patients, aged 6–16 years, with allergic rhinitis. In these children, chlorpheniramine had a mean elimination half-life of 13.1 ± 6.6 h, a mean clearance rate of 7.23 ± 3.16 mL/min/kg, and a mean apparent volume of distribution of 7.0 ± 2.8 L/kg. Over 48 h, the recovery in urine was as follows: chlorpheniramine, 11.3 ± 6.7%; demethylchlorpheniramine, 23.3 ± 11.1%; and didemethylchlorpheniramine, 9.6 ± 9.4%. Urine flow rate and urine pH were uncontrolled and ranged from 2.2 to 113.3 mL/h and 5.1–7.9, respectively, over the 48-h period. In some children urine flow rate and pH were constant, while in others there was great variability. When drug and metabolite excretion rates *versus* both urine flow rates and pH values were analyzed by multiple linear regression, the results were significantly better ($p \leq 0.05$) than when each factor was analyzed independently. The excretion rate of chlorpheniramine and its two demethylated metabolites decreased as urine pH increased and urine flow rate decreased. This information must be considered in future pharmacokinetic studies of this drug.

Keyphrases □ Chlorpheniramine—demethylated metabolites, urinary excretion in children, pharmacokinetics □ Excretion, urinary—chlorpheniramine and its demethylated metabolites, children, pharmacokinetics □ Pharmacokinetics—urinary excretion of chlorpheniramine and its demethylated metabolites, children

Chlorpheniramine, a histamine H_1 receptor antagonist, has been used for over 30 years in the treatment of allergic rhinitis (1). Recently, the development of sensitive, specific HPLC (2) and GLC-MS (3) assays have facilitated bioavailability (4–6) and pharmacokinetic (7–9) studies with chlorpheniramine. The metabolism of chlorpheniramine has been investigated in dogs (10) and humans (11), and the effect of induced, constant urine pH and flow rate on the rate of excretion of the unchanged drug has been evaluated (12). In recent single- and multiple-dose urinary studies (9, 13, 14), no correlation was determined between uncontrolled urine pH and flow rate and chlorpheniramine excretion. We have recently modified an HPLC assay (2) for chlorpheniramine (I), demethylchlorpheniramine (II), and didemethylchlorpheniramine (III) and have studied the pharmacokinetics and efficacy of chlorpheniramine in children with severe perennial allergic rhinitis (15). In this single-dose study (15), timed urine samples were also collected and the effect of uncontrolled urine pH and flow rate on the excretion of chlorpheniramine and two of its metabolites was evaluated.



I: $R_1 = R_2 = CH_3$
II: $R_1 = CH_3$, $R_2 = H$
III: $R_1 = R_2 = H$

EXPERIMENTAL

Patients—Chlorpheniramine was given to 11 patients with allergic rhinitis, mean age 11.0 ± 3.0 years and mean weight 39.6 ± 9.2 kg. All patients had received regular chlorpheniramine treatment for at least 6 months during the course of their rhinitis, but no patient had received it within 1 month of study. The protocol for this investigation was approved by the Faculty Committee of the University of Manitoba on the Use of Human Subjects in Research, and signed informed consent was obtained from the parents and the child before the study.

Protocol—Children reported to the Children's Hospital Clinical Investigation Unit at 0800 hours after an overnight fast. They had not received any medications in the preceding 72 h and were examined for nasal symptoms. After placement of an indwelling intravenous needle and withdrawal of 2 mL of blood, each patient received a single 0.12-mg/kg dose of a commercially available chlorpheniramine maleate syrup[1] with 120 mL of water. Uniform meals and snacks were served throughout the study, beginning 2 h after drug ingestion, and standardized activities were provided. Additional blood samples were obtained from the indwelling needle 1, 3, 6, 9, 12, 15, 18, 24, and 30 h after chlorpheniramine ingestion. The serum was separated and frozen at −20°C until the samples were analyzed. Urine samples were collected and pooled every 6 h for up to 48 h. The pooled samples were mixed well and measured; an aliquot was removed and frozen at −20°C until the samples were analyzed. The pH was determined on each aliquot prior to drug analysis.

Liquid Chromatographic Analysis of Chlorpheniramine (I), Demethylchlorpheniramine (II), and Didemethylchlorpheniramine (III)—One milliliter of test serum, urine, or control serum or urine containing standards was transferred into a 16 × 100-mm test tube, and 100 μL of internal standard solution (brompheniramine maleate, 1 μg/mL) was added. To this, 250 μL of 5% KOH and 5 mL of ether were added; the sample was mixed in a vortex mixer for 20 s and centrifuged for 1 min to separate the layers. The ether layer was transferred to a new 16 × 100-mm test tube containing 0.5 mL of 0.5% phosphoric acid, mixed, and centrifuged as before. With the aid of a methanol–dry ice bath, the aqueous layer was frozen and the ether layer discarded. When the aqueous layer was completely thawed the sample was made alkaline with 250 μL of 5% KOH and extracted with 5 mL of ether again as before. The ether layer was transferred to a dry 13 × 100-mm test tube and evaporated at 25°C with the aid of dry nitrogen. The sample was redissolved in 100 μL of mobile phase, and 25–100 μL were injected directly into the HPLC.

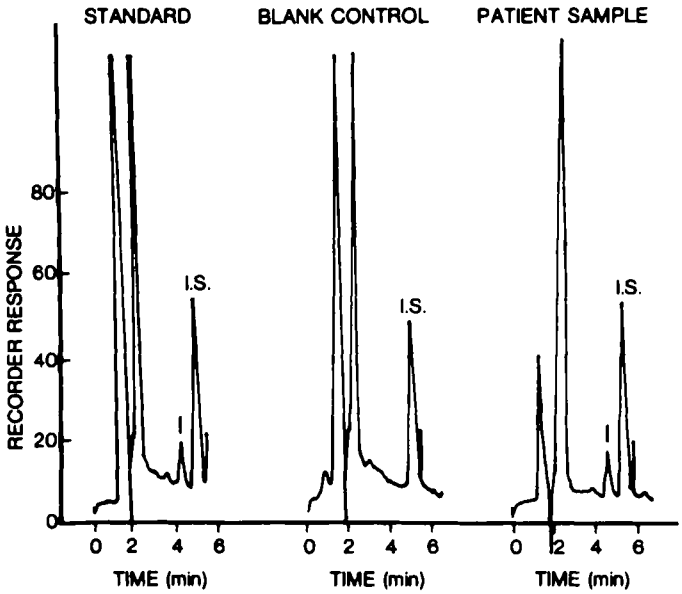


Figure 1—*Chromatograms of chlorpheniramine (I) and the internal standard (IS) in serum.*

[1] Chlortripolon Syrup; Schering Canada, Inc.

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Table I—Serum Chlorpheniramine Levels in Children Following a 0.12-mg/kg Oral Dose of Chlorpheniramine Maleate

Patient	Chlorpheniramine Level, ng/mL									
	0 h	1 h	3 h	6 h	9 h	12 h	15 h	18 h	24 h	30 h
11	5.1	17.7	15.8	13.1	11.9	11.8	9.0	7.4	7.4	—[a]
5	0	8.4	18.5	12.8	9.4	10.0	7.9	9.3	8.9	5.7
1	0.8	5.6	13.5	8.0	5.3	5.5	5.3	3.2	1.9	0
4	0	8.7	10.5	8.1	5.2	4.5	3.1	1.5	1.1	0
7	0	17.1	11.7	8.8	7.4	6.7	3.4	2.4	2.3	1.2
8	0	12.0	12.0	9.6	6.3	—	4.4	—	2.7	1.8
2	0	5.6	14.1	8.2	6.1	5.1	3.5	2.7	1.7	0
9	0	14.5	12.0	13.5	12.1	8.6	6.0	—	7.6	4.5
3	0	8.4	7.8	7.4	5.5	5.9	3.1	2.5	2.3	1.2
10	0	6.1	8.0	6.5	5.9	4.2	4.0	3.5	3.4	2.4
6	0	2.5	9.2	13.9	9.8	10.1	9.8	6.9	6.2	5.6
Mean		9.7	12.1	10.0	7.8	7.2	5.4	4.4	4.1	2.3
±SD		5.0	3.3	2.8	2.7	2.7	2.5	2.8	2.8	2.3

[a] — Sample not collected.

A component HPLC system was used, consisting of an injector, a high-pressure pump, an absorbance detector with a fixed wavelength of 254 nm, and a data module[2]. A 30 × 0.39-cm reverse-phase C_{18} stainless steel column[3] was used. The mobile phase was 25% acetonitrile in 0.075 M phosphate buffer (NaH_2PO_4), pH 2.5 (with H_3PO_4). At a flow rate of 2 mL/min, retention times were: didemethylchlorpheniramine, 2.7 min; demethylchlorpheniramine, 3.2 min; chlorpheniramine, 4.3 min; and internal standard, 5.0 min. With this procedure, drug concentrations as low as 1 ng/mL were measured.

Pharmacokinetic Data—After the initial absorption peak there was a second lower peak on all the serum chlorpheniramine concentration *versus* time plots. There were a limited number of data points, so most of the pharmacokinetic values were determined by model-independent methods (16). It was possible to determine a serum half-life by fitting the terminal linear portion of each curve to

$$C_p = C_p^0 e^{-k_e t} \qquad \text{(Eq. 1)}$$

using the BMDP[4] computer program where C_p is the serum concentration at any time t, C_p^0 is the serum concentration extrapolated to time zero (t^0), and k_e is the first-order elimination rate constant. The elimination half-life ($t_{1/2}$) was then calculated from:

$$t_{1/2} = \frac{\ln 2}{k_e} \qquad \text{(Eq. 2)}$$

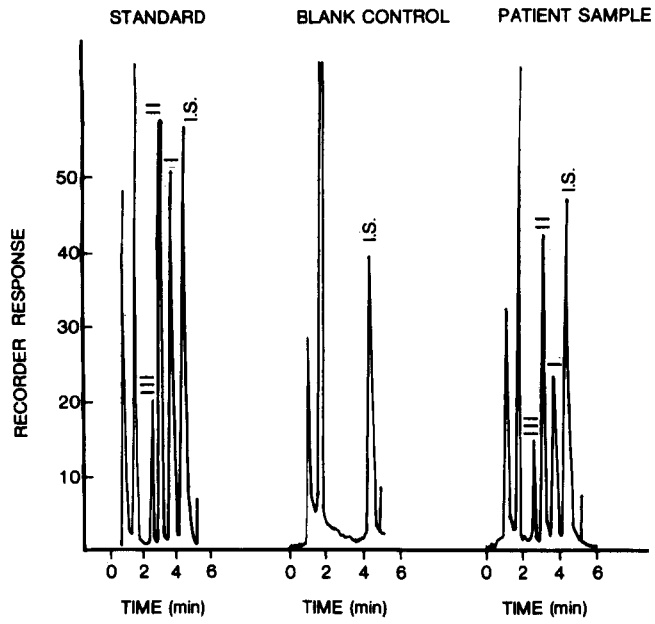

Figure 2—*Chromatograms of chlorpheniramine (I), demethylchlorpheniramine (II), didemethylchlorpheniramine (III), and the internal standard (IS) in urine.*

Total body clearance (CL) was calculated using:

$$CL = \frac{f \cdot \text{Dose}}{\text{AUC}} \qquad \text{(Eq. 3)}$$

where f is the fraction of the dose adsorbed and AUC is the area under the serum chlorpheniramine concentration *versus* time curve, calculated using the trapezoidal rule to time t_n, to which the value C_{p_n}/k was added to extrapolate to infinite time. The apparent volume of distribution (Vd) was calculated using:

$$Vd = \frac{CL}{k_e} \qquad \text{(Eq. 4)}$$

The excretion rate (ER) of chlorpheniramine and its two demethylated metabolites was calculated using:

$$\text{ER} = \frac{dX_u}{dt} \qquad \text{(Eq. 5)}$$

where dX_u was approximated by ΔX_u or the average hourly amount excreted, calculated from each 6-h urine aliquot, and dt or Δt was 1 h. The urine flow rate (UFR) was calculated using:

$$\text{UFR} = \frac{dV_u}{dt} \qquad \text{(Eq. 6)}$$

where V_u was the volume of urine voided in the 6-h period averaged to an hourly rate.

Statistical Analysis—Correlations between urine pH, flow rate, and excretion rate of chlorpheniramine or its two demethylated metabolites were determined using multiple linear regression analyses (17). Results were evaluated using the Student's paired and unpaired t tests (17). All calculations were performed on a programmable calculator[5].

RESULTS AND DISCUSSION

Typical chromatograms of chlorpheniramine (I) in serum are shown in Fig. 1. Chromatograms of I, II, and III in urine are shown in Fig. 2. Calibration curves constructed by plotting the peak height ratio of I from serum to internal standard *versus* I concentration were linear ($r = 1.00$) over the concentration range of 0–30 ng/mL. Compounds I, II, and III extracted from urine also yielded linear calibration curves when the peak height ratio of compound to internal standard was plotted *versus* concentration. The slopes and intercepts of the calibration curves did not vary significantly throughout the period of analysis of all samples from this study. Serum chlorpheniramine concentrations are shown in Table I.

The results of pharmacokinetic studies for each subject are shown in Table II. The mean elimination half-life for I of 13.1 ± 6.6 h obtained in the study (15) was not significantly different ($p = 0.05$) from the mean value of 9.6 ± 3.6 h found in seven children given an intravenous dose of this drug (8). In adults, a wide range of elimination half-life values have been reported following oral (4–6) and intravenous (7, 9) administration. The half-life values in four studies, 20.96 ± 4.94 h (4), 25.1 ± 8.4 h (5), 24.4 ± 6.6 h (7), and 27.9 ± 8.7 h (9), were significantly longer ($p \leq 0.05$) than the values in children. However, half-life values of 17.3 ± 4.4 and 14.6 ± 3.4 h in another study in adults (6) were not significantly different ($p = 0.05$). Since some of the subjects in this latter study were <20 years of age, it is probable that elimination rates for I are age dependent.

[2] U6K injector, 6000A pump, 440 absorbance detector, and a 7000 data module; Waters Associates, Milford, Mass.
[3] μBondapak; Waters Associates, Milford, Mass.
[4] BMDP-77, University of California Press, Berkeley, 1977.
[5] HP-67; Hewlett-Packard, Corvalis, Ore.

Table II—Pharmacokinetic Parameters Calculated for Children Following a 0.12-mg/kg Oral Dose of Chlorpheniramine Maleate

Patient	Sex	Age, year	Weight, kg	k_e, h^{-1}	$t_{1/2}$, h	AUC, ng/mL/h	CL, mL/min/kg	Vd, L/kg	C_{max}, ng/mL	t_{max}, h
11	F	6	29.0	0.04	17.3	432.56	3.62	4.9	17.7	1
5	M	8	40.5	0.04	17.3	430.37	3.26	4.9	18.5	3
1	M	8.5	28.3	0.11	6.3	149.48	10.68	5.8	13.5	3
4	M	9.5	32.9	0.11	6.3	117.15	12.02	6.6	10.5	3
7	F	10	49.5	0.06	11.6	173.34	8.06	8.1	17.1	1
8	M	10	29.5	0.06	11.6	187.94	7.51	7.5	12.0	1
2	M	12.5	39.3	0.09	7.7	145.37	9.63	6.4	14.1	3
9	M	13	38.0	0.09	7.7	303.38	4.64	3.1	14.5	1
3	M	13	54.6	0.06	11.6	141.85	10.07	10.1	8.4	1
10	F	14	44.3	0.03	23.1	211.58	6.63	13.3	8.0	3
6	F	16	50.0	0.03	23.1	414.75	3.39	6.8	13.9	6
Mean		11.0	39.6	0.07	13.1	246.16	7.23	7.0	13.5	2.5
±*SD*		3.0	9.2	0.03	6.6	125.42	3.16	2.8	3.5	1.5

Chlorpheniramine was only administered orally to the children in this study, so it was not possible to calculate the absolute bioavailability. The uncorrected values for clearance and volume of distribution were 7.23 ± 3.16 mL/min/kg and 7.0 ± 2.8 L/kg, respectively. When clearance values were calculated using a fraction of the dose absorbed of 0.6 (9), the mean value (4.32 ± 1.92 mL/min/kg) was not significantly different ($p = 0.05$) from the value of 5.39 ± 1.45 mL/min/kg obtained from a previous study in children (8) in which the dose was given intravenously. It was significantly different ($p \leq 0.05$) from the clearance rate of 7.92 ± 1.81 mL/min/kg found in one other study in adults (7), in which there was wide scatter in the serum chlorpheniramine concentrations *versus* time plots.

Using the same 0.6 fraction of dose absorbed (9), the mean apparent volume of distribution was 4.2 ± 1.6 L/kg. This value was not significantly different ($p = 0.05$) from those of 4.30 ± 1.26 (8) and 3.4 ± 0.3 L/kg (9) obtained in children and adults, respectively, given an intravenous dose of I. The uncorrected volume of distribution value of 7.0 ± 2.8 L/kg obtained in these 11 children was also not significantly different ($p = 0.05$) from uncorrected values of 7.6 ± 2.1 L/kg reported previously in adults (4).

The urinary excretion of I and its metabolism to II and III has been reported (13) and confirmed (11). The recovery of unchanged drug and metabolites in 48-h urine samples is shown in Table III. The urine flow rate, pH, and excretion rate values for I, II, and III for each subject are shown in Table IV. Representative plots of urine flow rate, pH, and excretion rates of chlorpheniramine and its two demethylated metabolites *versus* time are shown in Fig. 3. Urine flow rates and pH were not controlled in this study and ranged from 2.2 to 113.3 mL/h and 5.1–7.9, respectively, over the 48-h study period. In some of the children, urine flow rate and pH were constant (Fig. 3a), while in others they were quite variable (Fig. 3b).

Since urine collection intervals varied from study to study (12–14) it was difficult to compare drug recoveries. In adults, recoveries of unchanged drug in 24-h pooled urine samples were 4.5–11% (12), 5.2% (13), and 5.5–15% (14) as compared with 11.29 ± 6.68% (4.13–25.62%) in 48 h in these children. In adults 10.4% (14) and 13.2% (13) was recovered as demethylchlorpheniramine in 24 h compared with 23.30 ± 11.06% (8.40–45.51%) in 48 h in this study. The didemethylchlorpheniramine accounted for only 3.6% (14) and 5.8% (13) of the dose in adults in 24 h, while 9.60 ± 9.44% (1.20–29.20%) of the dose was recovered in the young patients in 48 h. The results were similar despite the differences in the collection intervals. In the present study, 44.19 ± 19.10% (18.60–73.45%) of the dose was recovered in 48 h. However, since only four subjects had half-life values <8 h and some had half-life values as long as 23 h, it is not valid to assume that the 48-h recovery accounts for all drug and metabolites in urine following this single oral dose. In the four subjects with half-life values <8 h, 48-h urinary recovery ranged from 35.18 to 66.29%. The missing 34–65% of the dose was assumed to be eliminated as unextractable metabolites (14). In the dog, oxidative deamination accounted for a fraction of these metabolites, as 11% was identified as 3-(*p*-chlorobenzyl)-3-(2-pyridyl)propanol and 18% as the corresponding propionic acid (10). These metabolites have not been identified in humans (11).

Table III—Percentage of a 0.12-mg/kg Oral Dose of Chlorpheniramine Maleate Recovered in Urine at 48 h

Patient	Dose,[a] mg	III[b], %	II[c], %	I, %	Dose Recovered in 48 h, %
11	2.45	2.32[d]	45.51[d]	25.62[d]	73.45[d]
5	3.41	1.90	13.16	12.90	28.20
1	2.71	23.29	33.20	9.81	66.29
4	2.78	8.80	22.25	4.13	35.18
7	4.15	29.20	34.13	5.50	68.86
8	2.50	15.20	29.80	14.90	59.84
2	3.30	11.48	20.07	4.63	36.15
9	3.21	1.62	15.82	19.74	37.17
3	4.68	6.05	16.29	7.12	29.46
10	3.73	4.57	17.42	10.88	32.87
6	4.22	1.20	8.40	9.00	18.60
Mean	3.38	9.60	23.30	11.29	44.19
±*SD*	0.75	9.44	11.06	6.68	19.10

[a] As chlorpheniramine (I) free base. [b] Percent of dose recovered as didemethylchlorpheniramine (III), expressed as chlorpheniramine equivalents. [c] Percent of dose recovered as demethylchlorpheniramine (II), expressed as chlorpheniramine equivalents. [d] Control urine from this patient showed traces of chlorpheniramine and metabolites by HPLC and TLC.

The effect of urine pH and flow rate on the excretion of chlorpheniramine and its metabolites has been reported following single- and multiple-dose studies (12–14). When the urine was acidic, significantly more chlorpheniramine was excreted as unchanged drug than when the urine was alkaline (12–14). In addition, although the demethyl metabolite was similarly affected,

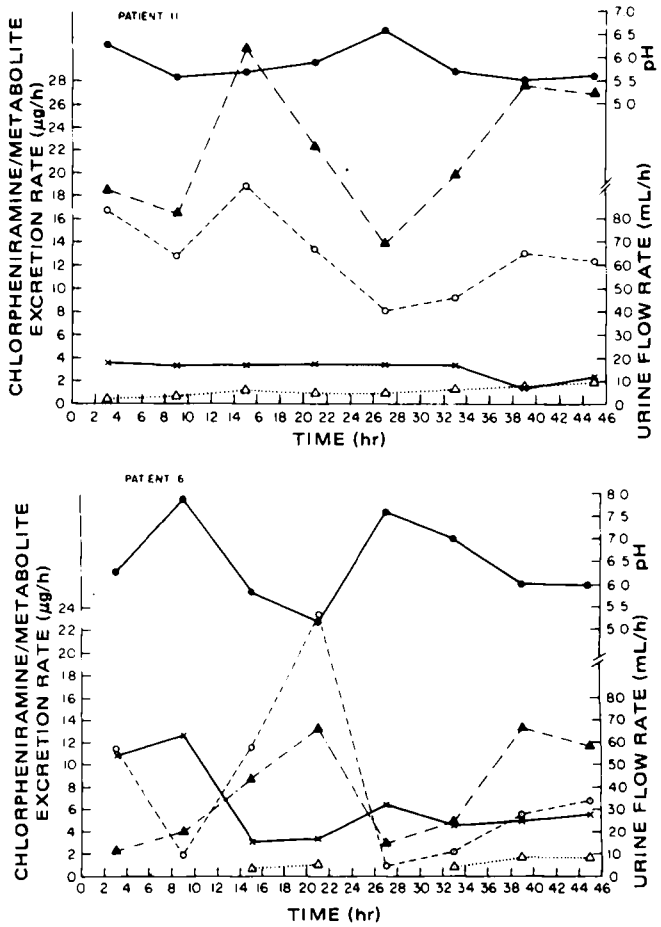

Figure 3—*Urinary excretion rates (μg/h) of chlorpheniramine (⊙), demethylchlorpheniramine (▲), and didemethylchlorpheniramine (△), urine flow rates (mL/h) (×), and urine pH (●) plotted* versus *time in young subjects given 0.12 mg/kg of drug orally.*

Table IV—Urine Flow Rates, pH, and Excretion Rates of Chlorpheniramine (I), Demethylchlorpheniramine (II), and Didemethylchlorpheniramine (III) in 11 Patients Given a 0.12-mg/kg Oral Dose of Chlorpheniramine Maleate

Patient		Time, h							
		6	12	18	24	30	36	42	48
1	Urine flow rate, mL/h	45.0	20.0	8.3	9.2	17.5	13.3	16.7	8.3
	pH	6.5	5.3	5.3	5.5	5.9	5.5	5.5	5.2
	Excretion rate, μg/h								
	I	4.8	15.1	10.0	6.4	1.9	2.5	2.0	1.7
	II	6.9	29.2	21.5	17.8	15.3	17.6	20.9	13.1
	III	4.0	15.5	11.7	10.6	9.1	12.8	18.9	11.5
2	Urine flow rate, mL/h	103.3	50.0	45.8	24.2	57.5	21.3	63.3	40.0
	pH	6.8	6.5	6.5	5.6	6.9	6.7	6.1	5.2
	Excretion rate, μg/h								
	I	10.7	4.0	3.4	3.6	1.1	0.4	1.4	1.0
	II	10.8	18.8	21.2	28.0	8.7	4.4	13.0	18.8
	III	2.8	6.0	8.3	13.5	5.3	4.2	13.6	19.2
3	Urine flow rate, mL/h	113.3	34.2	35.0	33.3	69.2	48.3	60.8	42.5
	pH	5.6	5.3	5.3	5.6	7.3	7.0	6.6	6.0
	Excretion rate, μg/h								
	I	10.6	22.5	12.0	4.8	1.3	1.3	1.2	1.9
	II	8.5	23.5	26.2	22.5	7.6	6.8	12.8	12.9
	III	2.8	3.9	5.9	5.7	3.1	3.8	8.3	8.7
4	Urine flow rate, mL/h	83.3	53.3	35.8	25.0	38.3	35.0	18.3	37.5
	pH	7.2	6.6	6.0	5.7	7.0	6.5	5.8	5.5
	Excretion rate, μg/h								
	I	4.6	3.3	4.8	3.9	—	0.77	0.55	1.3
	II	6.2	12.9	21.9	22.6	6.2	9.2	6.6	12.4
	III	0.0	3.3	5.2	7.3	2.5	4.5	4.1	9.5
5	Urine flow rate, mL/h	52.5	21.6	18.3	22.5	17.5	19.2	14.2	34.2
	pH	6.3	5.6	5.7	6.1	5.7	5.9	5.9	6.0
	Excretion rate, μg/h								
	I	10.2	16.7	13.6	9.3	6.8	5.7	4.1	7.3
	II	2.6	5.7	11.7	9.3	8.2	5.7	7.1	19.8
	III	0.4	0.5	1.0	1.0	1.0	1.3	1.1	3.2
6	Urine flow rate, mL/h	54.2	63.3	15.0	16.7	31.7	23.3	25.0	26.7
	pH	6.3	7.9	5.8	5.2	7.6	7.0	6.0	6.0
	Excretion rate, μg/h								
	I	11.4	1.9	11.5	23.3	0.9	2.2	5.5	6.7
	II	2.3	3.9	8.7	13.2	3.0	4.9	13.3	11.7
	III	0.0	1.6	0.7	1.0	0.2	0.8	1.7	1.7
7	Urine flow rate, mL/h	97.5	35.8	18.3	13.3	113.3	105.3	22.5	42.5
	pH	6.6	7.6	6.2	5.4	7.3	7.0	6.7	6.8
	Excretion rate, μg/h								
	I	7.0	1.7	7.6	8.2	2.7	3.5	2.0	5.7
	II	12.1	11.8	37.2	36.4	22.4	32.0	23.4	48.8
	III	12.2	9.5	31.5	30.1	8.6	22.0	7.8	61.4
8	Urine flow rate, mL/h	71.7	30.8	23.0	29.2	20.0	68.3	18.3	18.3
	pH	6.2	5.2	5.6	5.0	5.2	6.3	5.6	5.1
	Excretion rate, μg/h								
	I	16.3	15.7	5.4	9.8	8.1	3.3	0.9	2.5
	II	13.7	18.0	18.2	21.5	15.0	10.3	12.1	15.4
	III	7.0	7.5	8.2	10.4	6.5	5.5	7.5	10.7
9	Urine flow rate, mL/h	91.7	30.0	14.7	15.0	8.3	35.0	2.2	16.7
	pH	7.3	6.2	5.6	6.0	5.9	7.2	6.6	5.9
	Excretion rate, μg/h								
	I	7.2	21.2	28.6	18.0	4.5	3.9	10.3	11.9
	II	6.3	9.5	14.1	12.0	3.9	6.1	14.5	14.1
	III	2.4	1.1	0.9	0.6	0.3	0.7	0.9	0.8
10	Urine flow rate, mL/h	58.3	29.2	25.0	25.0	33.3	33.3	16.7	18.3
	pH	6.2	6.6	6.0	5.7	6.1	6.6	6.1	5.7
	Excretion rate, μg/h								
	I	17.6	25.1	6.9	7.5	2.6	1.7	2.8	3.4
	II	9.8	8.1	16.4	21.7	11.0	8.8	13.9	13.1
	III	1.2	1.2	2.9	4.8	3.1	3.1	5.4	3.8
11	Urine flow rate, mL/h	18.3	16.7	16.7	17.5	16.7	16.7	6.7	11.7
	pH	6.3	5.6	5.7	5.9	6.6	5.7	5.5	5.6
	Excretion rate, μg/h								
	I	16.8	12.8	18.9	13.4	8.1	9.2	13.0	12.3
	II	18.5	16.5	30.9	22.3	13.9	19.8	27.5	26.9
	III	0.4	0.5	1.2	0.9	0.9	1.3	1.6	1.9

the excretion of the didemethyl metabolite appeared to be minimally affected by pH (14). When urinary pH was maintained in the acidic range, the urinary excretion of unchanged chlorpheniramine was dependent on urine flow rate. This effect can be explained by the theory that the epithelium of the distal convoluted kidney tubules is selectively permeable to the unionized base (12). The effect of urine flow rate on the two demethylated metabolites has not been evaluated to date.

To evaluate the effect of urine flow rate and pH on the excretion rate of I, II, and III, a comparison was made between linear regression analyses of excretion rate *versus* urine flow rate and excretion rate *versus* urine pH and multiple linear regression analysis of excretion rate *versus* both urine flow rate and pH. These calculations were performed on all experimental values and on results obtained after 12 h only. It was assumed that chlorpheniramine absorption would be complete by this time and that a better correlation might be obtained in the postabsorption phase. The correlation coefficients (r) calculated for the single and multiple regression analyses are shown in Table V.

For chlorpheniramine, the mean results obtained from the postabsorption data were virtually identical to the mean results obtained from the total data. The mean correlation coefficient obtained from the multiple linear regression analysis, $r = 0.66 \pm 0.15$, was significantly better ($p \leq 0.05$) than the values obtained from the urine flow rate data, $r = 0.32 \pm 0.21$, and from the urine

Table V—Correlation Coefficients Calculated from Single and Multiple Linear Regression Analysis of Excretion Rate *versus* Urine Flow Rate and Urine pH in 11 Patients Given a 0.12-mg/kg Oral Dose of Chlorpheniramine Maleate

	Chlorpheniramine (I)						Demethylchlorpheniramine (II)						Didemethylchlorpheniramine (III)					
	Multiple Regressions[a]		Urine Flow Rate		Urine pH		Multiple Regressions[a]		Urine Flow Rate		Urine pH		Multiple Regressions[a]		Urine Flow Rate		Urine pH	
Patient	All[b]	>12 h[c]	All	>12 h	All	>12 h	All	>12 h	All	>12 h	All	>12 h	All	>12 h	All	>12 h	All	>12 h
1	0.60	0.66	0.02	0.61	0.27	0.33	0.75	0.24	0.48	0.06	0.11	0.09	0.75	0.89	0.54	0.33	0.73	0.22
2	0.75	0.23	0.75	0.12	0.29	0.22	0.65	0.67	0.05	0.19	0.64	0.19	0.95	1.00	0.37	0.07	0.88	0.96
3	0.75	0.79	0.20	0.65	0.75	0.79	0.93	0.95	0.66	0.76	0.78	0.94	0.43	0.58	0.42	0.26	0.09	0.47
4	0.54	0.26	0.52	0.18	0.36	0.14	0.57	0.53	0.32	0.00	0.56	0.48	0.90	0.94	0.63	0.06	0.90	0.82
5	0.68	0.39	0.43	0.11	0.35	0.07	0.11	0.96	0.11	0.92	0.10	0.08	0.10	0.92	0.06	0.91	0.10	0.38
6	0.85	0.87	0.36	0.77	0.83	0.85	0.80	0.98	0.66	0.43	0.77	0.90	0.11	0.81	0.06	0.06	0.11	0.58
7	0.85	0.83	0.26	0.60	0.83	0.82	0.48	0.39	0.34	0.38	0.47	0.34	0.38	0.32	0.31	0.32	0.34	0.23
8	0.69	0.71	0.38	0.78	0.00	0.49	0.77	0.75	0.44	0.45	0.72	0.73	0.70	0.77	0.53	0.54	0.70	0.77
9	0.70	0.86	0.30	0.35	0.63	0.28	0.46	0.59	0.37	0.13	0.46	0.32	0.98	0.69	0.94	—	0.59	0.06
10	0.53	0.66	0.45	0.20	0.41	0.63	0.81	0.74	0.44	0.39	0.79	0.73	0.79	0.68	0.72	0.68	0.58	0.37
11	0.34	0.58	0.11	0.45	0.21	0.51	0.68	0.82	0.51	0.43	0.24	0.82	0.74	0.82	0.73	0.73	0.52	0.70
Mean	0.66	0.62	0.32	0.34	0.45	0.46	0.64	0.62	0.40	0.48	0.51	0.50	0.69	0.77	0.38	0.39	0.51	0.51
±*SD*	0.15	0.23	0.21	0.27	0.27	0.27	0.23	0.32	0.19	0.28	0.26	0.30	0.24	0.19	0.28	0.29	0.33	0.28

[a] Excretion rate to both urine flow rate and pH. [b] Analysis on all data points. [c] Analysis on data points after 12 h only (assuming oral absorption was complete).

pH data, $r = 0.45 \pm 0.27$. The dependence of chlorpheniramine excretion rate on both urine flow rate and urine pH, even in patients where these parameters were not controlled, was clearly demonstrated.

The results obtained from the regression analysis of the demethylchlorpheniramine data were similar. There was no difference between results obtained from the postabsorption data and the total data. The mean correlation coefficient from the multiple linear regression analysis, $r = 0.64 \pm 0.23$, was significantly better ($p \leq 0.05$) than the value from the urine flow rate data, $r = 0.40 \pm 0.19$, but not significantly improved ($p = 0.05$) from the urine pH data, $r = 0.51 \pm 0.26$. Demethylchlorpheniramine appeared to be more dependent on urine pH than on urine flow rate.

For didemethylchlorpheniramine, the mean correlation coefficient for multiple linear regression analysis from the total data, $r = 0.69 \pm 0.24$, was not significantly improved ($p = 0.05$) from the results obtained for urine flow rate, $r = 0.38 \pm 0.28$, or urine pH, $r = 0.51 \pm 0.33$. However, for the postabsorption phase data, the mean multiple linear regression analysis correlation coefficient, $r = 0.77 \pm 0.19$ was significantly better ($p \leq 0.05$) than that obtained from the urine flow rate data, $r = 0.39 \pm 0.29$, or from the urine pH data, $r = 0.51 \pm 0.28$. Didemethylation is probably a sequential metabolic pathway so this metabolite would be formed from demethylchlorpheniramine and would be dependent on the rate of formation of demethylchlorpheniramine from chlorpheniramine. For this reason, the results from the data after 12 h were more consistent ($r = 0.77 \pm 0.19$) than those obtained from the total data ($r = 0.69 \pm 0.24$). From that time, absorption of chlorpheniramine would probably be complete, and the rate of demethylchlorpheniramine formation would be constant or steadily decreasing as the amount of chlorpheniramine decreased.

These results confirm that the chlorpheniramine excretion rate is dependent on urine flow rate and pH (12–14). Demethylchlorpheniramine appears to be more dependent on urine pH than on urine flow rate, and didemethylchlorpheniramine may also be dependent on both urine flow rate and pH. Since urine pH has been reported to have a minimal effect on didemethylchlorpheniramine excretion (14), further studies are required to confirm these findings.

Currently recommended doses for chlorpheniramine are 4–8 mg four times daily. The results of this study, the long chlorpheniramine half-life values (4–9, 15), and the prolonged biological effects (15) of chlorpheniramine suggest that in current dosage regimens chlorpheniramine may be prescribed more frequently than required to produce beneficial effects while minimizing adverse effects. In patients where urine pH may be chronically elevated and urine flow rate reduced, elimination of both the unchanged chlorpheniramine and its metabolites may be further decreased.

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