Urinary Excretion of Pheniramine and Its *N*-Demethylated Metabolites in Man—Comparison with Chlorpheniramine and Brompheniramine Data

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The *N*-demethylated metabolites of pheniramine, *N*-desmonomethylpheniramine and *N*-desdimethylpheniramine, were found in the urine of a male subject using a repetitive dosage schedule. A comparison of the urinary excretion data of pheniramine and its halogenated derivatives indicated the compounds to be metabolized in the following order: pheniramine < chlorpheniramine < brompheniramine. This is inverse to the order of total free and *N*-demethylated drug excreted in the urine.

ALTHOUGH THE URINARY EXCRETION of chlorpheniramine (1, 2) and brompheniramine (3) have been studied, no such study has been made on the urinary excretion of pheniramine.[1]

The present investigation was undertaken to further determine the substituent effect of the halogens in the *p*-halobenzyl group of the pheniramines on urinary excretion.

EXPERIMENTAL[2]

Protocol—A male subject [used in the previous chlorpheniramine study (2)] under a normal diet with no urine pH or fluid intake control was used in this study.

Single Dose Regimen—The subject orally took a single dose of 74 mg. of pheniramine maleate in tablet form (two 37-mg. pheniramine maleate tablets). Urine was collected normally for 6 days and combined into 24-hr. samples.

Multiple Dose Regimen—The same subject orally took 37 mg. of pheniramine maleate in tablet form daily for 21 days. Urine was collected normally for 25 days and combined into 24-hr. samples.

Analytical Methods—A gas chromatographic method previously described (2, 4) was used. The column was operated at 170°. A 2.5-ft. column exhibited 1,500 theoretical plates for pheniramine.

Free pheniramine had a retention time of 7.0 min. Quantitative determinations were made using a pheniramine reference standard. Isolation by thin-layer chromatography on alumina (5) and subsequent mass spectroscopy (6) showed an *m/e* value of 58 for $CH_2{=}N(CH_3)_2$ indicative of a tertiary amine and *m/e* values of 169 and 83.5 which are characteristic of the benzyl-2-pyridyl group. It did not form derivatives either with cyclopentanone or acetone using the procedure of Capella and Horning (7).

Metabolite *X* had a retention time of 13 min. Quantitative determinations *via* the area technique were made using pheniramine as a calibration standard. Isolation by thin-layer chromatography on alumina (5) and mass spectroscopy (6) showed *X* to be a secondary amine with an *m/e* of 44 for $CH_2{=}NH(CH_3)$ and the *m/e* values of 169 and 83.5 for the benzyl-2-pyridyl group. It formed a derivative (retention time > 60 min.) with cyclopentanone (indicative of primary and secondary amines), but none with acetone (indicative of the absence of a primary amine).

Metabolite *Y* had a retention time of 18 min. Quantitative determinations *via* the area technique were made using pheniramine as a calibration standard. Isolation by thin-layer chromatography on alumina (5) failed to separate metabolite *Y* from the fiftyfold excess of metabolite *X*, consequently no mass spectral data could be obtained. It formed derivatives with cyclopentanone (retention time > 60 min.) and with acetone (retention time, 22 min.), indicative of a primary amine.

Lipid-Water Distribution—The procedure of McMahon (8) was used to determine the partition coefficient of pheniramine, chlorpheniramine, and brompheniramine for the heptane and pH 7.4 aqueous phosphate buffer system.

RESULTS AND DISCUSSION

Single Dose Regimen—The urinary excretion of free pheniramine by the subject on the single dose regimen is shown in Table I.

The amount of unchanged pheniramine excreted by the single subject in the first 24 hr. was 16.6% of the ingested dose. The total excretion of free pheniramine (over the 6-day period) was 22.6% of the ingested dose.

TABLE I—URINARY EXCRETION OF FREE PHENIRAMINE BY SUBJECT WHO RECEIVED ONE DOSE OF TWO 37-mg. PHENIRAMINE MALEATE TABLETS

Time After Drug Taken,[a] Days	Combined Volume of 24-Hr. Urine, ml.	pH of 24-Hr. Urine	Pheniramine[b] Excreted in 24-Hr. Urine, mg.
0	...	...	...
1	1420	6.2	12.26
2	1465	6.2	3.17
3	1065	5.9	0.90
4	970	6.0	0.25
5	1080	5.9	0.10
6	760	5.9	0.02

[a] Experiment started at 7:30 p.m. [b] Reported as pheniramine maleate.

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[1] Pheniramine is *dl*-2-[α-[2-(dimethylamino)ethyl]-benzyl] pyridine.

[2] All gas chromatograms were obtained on a F and M model 400 gas chromatograph with a flame ionization detector and a Minneapolis Honeywell recorder. The mass spectra were obtained on a Consolidated Electrodynamics Corporation model CEC-103C mass spectrometer.

Multiple Dose Regimen—The urinary excretion of free pheniramine by the subject on a multiple dose regimen is listed in Table II.

The 24-hr. urinary excretion rate did not form a gradually increasing pattern as in the case of chlorpheniramine (2) and brompheniramine (3), indicating that pheniramine is not building up in the body.

The calculated *average* daily excretion rate (for the first 21 days) of free pheniramine was 9.0 mg., or 24.3% of the repeated 37-mg. pheniramine dose. This compares favorably with the 22.6% which was obtained in the single dose experiment. Large fluctuations (coefficient of variation of 32%) were observed in the daily excretion rate which could not be accounted for by variance in daily urine pH and volume.

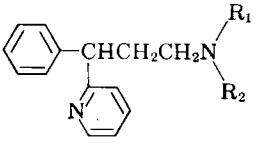
The average daily urine volume was 1,020 ml. (range: 655–1495 ml.) while the average daily urine pH was 6.1 (range: 5.5–6.6).

On termination of the drug intake regimen, the pheniramine excretion rate decreased. From the total amount of free pheniramine excreted after the last dose is taken on day 20 and using the average 9.0-mg. pheniramine excreted per 37-mg. dose, one can calculate the equivalent amount of pheniramine maleate present in the subject immediately after the last dose. This calculation yields a figure of 47 mg. of pheniramine maleate (equivalent to 1.3 tablets, each containing 37 mg. of pheniramine maleate). Since this is well within the daily urinary excretion variance, there is no evidence of drug build-up in the body under this multiple dosage regimen.

Metabolites *X* and *Y*—The metabolites *X* and *Y* were found to be *N*-desmonomethylpheniramine and *N*-desdimethylpheniramine, respectively (Table III).

During the first 21 days an average of 9.3 mg. *N*-desmonomethylpheniramine and 0.17 mg. *N*-desdimethylpheniramine were excreted daily (26.1% and 0.5% of the repeated 37-mg oral dose). Together with the free pheniramine excreted daily, this accounts for 51% of the dose leaving the fate of the remaining 49% still unaccounted for.

TABLE III—STRUCTURAL FORMULA OF PHENIRAMINE AND ITS METABOLITES



Compound	R_1	R_2
Pheniramine	CH_3	CH_3
Metabolite *X*	CH_3	H
Metabolite *Y*	H	H

TABLE II—URINARY EXCRETION OF FREE PHENIRAMINE AND ITS METABOLITES BY SUBJECT WHO DAILY RECEIVED ONE 37-mg. PHENIRAMINE MALEATE TABLET FROM DAY 0 TO DAY 20

Time,[a] Days	Combined Volume[b] of 24-Hr. Urine, ml.	pH of 24-Hr. Urine	Pheniramine[c] Excreted in 24-Hr. Urine, mg.	Metabolite *X*[d] Excreted in 24-Hr. Urine, mg.	Metabolite *Y*[e] Excreted in 24-Hr. Urine, mg.
0	...	...	...	...	...[f]
1	945	5.9	6.8	7.0	0.1
2	1215	6.6	6.1	8.2	0.1
3	1035	6.7	4.9	9.8	0.3
4	975	6.2	8.2	11.2	0.2
5	885	6.2	5.9	9.9	0.2
6	1110	6.2	11.2	11.3	0.2
7	1495	6.1	14.7	11.5	0.2
8	990	6.0	6.5	9.6	0.2
9	1110	6.4	7.7	5.4	0.1
10	655	5.8	11.8	7.6	0.1
11	740	5.6	12.2	8.8	0.1
12	1135	5.9	13.9	11.0	0.2
13	1295	6.2	11.5	11.4	0.2
14	785	6.1	10.6	10.0	0.2
15	1035	6.3	6.4	7.6	0.1
16	835	6.0	10.7	11.4	0.2
17	935	5.5	10.4	7.9	0.1
18	1065	5.9	7.2	7.7	0.1
19	1115	6.0	5.9	9.3	0.2
20	1135	6.1	8.8	10.3	0.2
21	940	5.9	7.4	7.8	0.2
22	720	5.6	2.8	3.5	0.1
23	1045	5.6	0.8	1.3	0.1
24	1270	6.0	0.3	0.4	0.0
25	820	5.5	0.2	0.0	0.0

[a] Underscored days 37 mg. of pheniramine maleate tablet ingested; experiment started at 7:30 p.m. [b] . . ., Sample not collected. [c] Reported as pheniramine maleate. [d] Reported as *N*-desmonomethylpheniramine maleate. [e] Reported as *N*-desdimethylpheniramine maleate. [f] . . ., Assay result not obtained.

TABLE IV—COMPARISON OF URINARY EXCRETION OF PHENIRAMINE, CHLORPHENIRAMINE, AND BROMPHENIRAMINE AND THEIR *N*-DEMETHYLATED METABOLITES IN MAN

Drug	% of Ingested Dose Excreted in Urine			
	Unchanged	*N*-Desmonomethyl-	*N*-Desdimethyl-	Total
Pheniramine	24.3	26.1	0.5	51
Chlorpheniramine	12.6	13.2	5.8	32
Brompheniramine	5.3	6.3	5.8	18

COMPARISON OF BROMPHENIRAMINE AND PHENIRAMINE WITH CHLORPHENIRAMINE

A comparison of the urinary excretion of pheniramine, chlorpheniramine, and brompheniramine and their *N*-demethylated metabolites is given in Table IV. The total urinary excretion of free pheniramine (24.3%) is greater, while that for free brompheniramine (5.3%) is less than that for chlorpheniramine (12.6%). This indicates that these drugs are metabolized (if one assumes that they are all well absorbed and there is no excretion of free drug *via* feces) in the following increasing order: pheniramine (76%), chlorpheniramine (87%), and brompheniramine (95%).

This difference in percentage metabolized may be due to differences in the degree of reabsorption from the kidney tubules by nonionic diffusion (9). Since the base strength of these amines are nearly identical (10), their lipid-water partition coefficient determines the degree of reabsorption. Using the heptane-water (pH 7.4) model, the distribution coefficients of these compounds were experimentally determined and tabulated in Table V. The drug with the highest lipid-water partition coefficient was brompheniramine followed by chlorpheniramine and pheniramine. These data are consistent with the amount of unchanged drug excreted in the urine.

TABLE V—COMPARISON OF LIPID-WATER DISTRIBUTION OF BROMPHENIRAMINE, CHLORPHENIRAMINE, AND PHENIRAMINE

Compd.	Heptane-Water Partition Coefficient[a]
Pheniramine	0.20
Chlorpheniramine	1.71
Brompheniramine	2.23

[a] 25°, water at pH 7.4.

It can be noted from Table IV that the amount of unchanged drug and *N*-desmonomethylated drug excreted are approximately equal for each of the three drugs. The reason for this is not obvious. The total amount of free drug plus *N*-demethylated metabolites excreted in the urine declined in the following order: pheniramine (51%), chlorpheniramine (32%), and brompheniramine (18%).

Urine pH and flow rate have been reported (1) to influence the renal excretion of chlorpheniramine. During the "steady state" period, the daily brompheniramine excretion rate was found to be dependent on the daily (24 hr.) urine pH and urine volume (3). These two variables (assuming a linear relationship) could account for 80% of the fluctuations in the daily free brompheniramine excretion rate. In the present study daily urine pH and urine volume could only account for about 25% of the fluctuations in the daily urinary excretion rate.

Repetitive daily oral dosage regimen appears to cause the build-up of brompheniramine in the body similar to the behavior of chlorpheniramine. However, in the case of pheniramine there is no evidence of drug build-up in the body.

SUMMARY AND CONCLUSIONS

A repetitive dosage regimen has been successfully used to identify two metabolites of pheniramine, *N*-desmonomethylpheniramine and *N*-desdimethylpheniramine, in the urine of a human.

The substitution of hydrogen for chlorine in chlorpheniramine evidently results in a molecule which is less extensively metabolized while the substitution of bromine for the same chlorine results in a molecule which is more extensively metabolized.

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Keyphrases

Pheniramine—urinary excretion
Metabolites, pheniramine—identification
Metabolism—pheniramine, chlorpheniramine, brompheniramine compared
Lipid–water partition coefficients
GLC—analysis