Influence of Partition Coefficient on Intestinal Absorption of Alkylamine Antihistamines

Keyphrases □ Absorption, GI—various alkylamine antihistamines, effect of partition coefficient, rats □ Partition coefficients—various alkylamine antihistamines, effect on GI absorption, rat □ Antihistamines, various alkylamine—GI absorption, effect of partition coefficient, rats

To the Editor:

Prior to initiating studies on the bioequivalence of various brands of chlorpheniramine maleate tablets, it was considered of value first to compare in animals the intestinal absorption of chlorpheniramine with that of brompheniramine and pheniramine to determine the overall absorption characteristics of the therapeutically useful alkylamine antihistamines.

The comparative absorption characteristics of these antihistamines as a group have not been studied in humans or animals, and such information would prove useful in the design of the experimental protocol and the subsequent assessment of bioavailability data in the bioequivalency studies.

The method of Doluisio *et al.* (1) was used to evaluate the intestinal absorption of each drug at pH 6.0. Aqueous phosphate buffer solutions of the maleate salts of pheniramine, chlorpheniramine, and brompheniramine were prepared at 25 mg/100 ml. Because of limited aqueous solubility, the tannate salt of chlorpheniramine was prepared at 7.5 mg/100 ml.

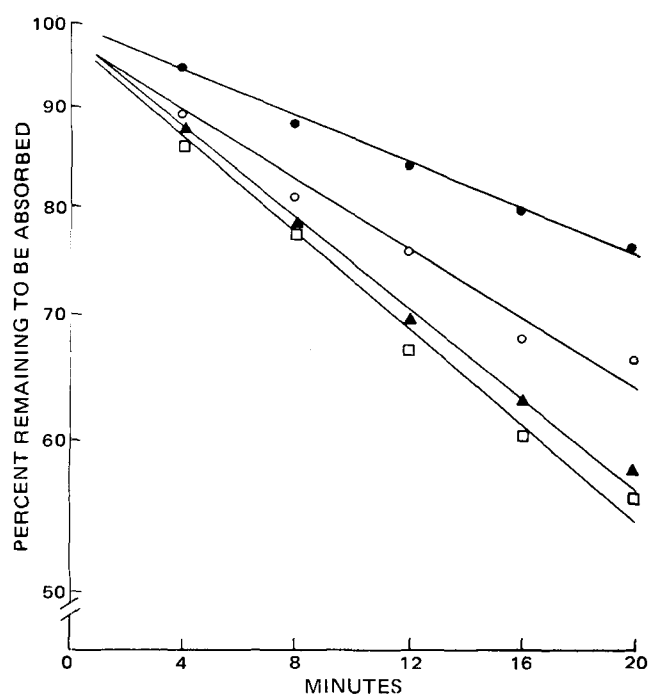

Figure 1—*Percent remaining to be absorbed as a function of time for the intestinal absorption of pheniramine maleate (●), chlorpheniramine tannate (○), chlorpheniramine maleate (▲), and brompheniramine maleate (□). Each data point represents the mean of three determinations.*

Table I—Absorption Half-Lives [a] and Partition Coefficients [b]

Drug	$t_{1/2}$, min	Partition Coefficient (pH 6.0) Heptane	Ether	Carbon Tetrachloride	Partition Coefficient (pH 7.5), Heptane
Pheniramine maleate	49.2	0.01	0.17	0.10	0.33
Chlorpheniramine tannate	32.9	0.10	0.60	1.04	—
Chlorpheniramine maleate	25.2	0.14	0.63	1.21	1.74
Brompheniramine maleate	23.7	0.16	0.64	2.04	3.16

[a] Measured at pH 6.0. [b] Measured at 25°.

The concentrations of the antihistamines in the phosphate buffer were determined by GLC analysis. Aqueous sample, 0.1 ml, was added to 4.0 ml of 0.12% NaOH (pH 12.2) in a 15-ml acid-washed glass centrifuge tube fitted with a polytef-lined cap. For the determination of chlorpheniramine and brompheniramine, 500 μl of chloroform containing 2.4 mg of pheniramine maleate/100 ml (as internal standard) was then added. The tubes were shaken and centrifuged, and 5 μl of the chloroform layer was injected directly onto the column. For the determination of pheniramine, the procedure outlined was repeated except that 500 μl of chloroform containing 5 mg of chlorpheniramine/100 ml (as internal standard) was substituted. The retention times for pheniramine, chlorpheniramine, and brompheniramine were 80, 121, and 153 sec, respectively.

The instrument[1] was equipped with a flame-ionization detector. Peak integration was measured with an electronic integrator[2]. Dual 1.8-m glass columns, 0.6-cm o.d., were packed with 2.5% SE-30 on 80–100-mesh Chromosorb G, DMCS. The nitrogen flow rate was 60 ml/min. Oven, injector, and detector temperatures were maintained at 240, 250, and 250°, respectively.

The results for the absorption of the antihistamines from the rat small intestine are shown in Fig. 1. Each alkylamine derivative was absorbed rather slowly at pH 6.0, with half-lives for first-order disappearance of drug from the lumen ranging from 24 min for brompheniramine to 49 min for pheniramine (Table I). Included in Table I are the heptane–phosphate buffer (pH 6.0) partition coefficients for each drug determined by the method of McMahon (2). As might be inferred from the absorption data of Fig. 1, the values of the partition coefficients were generally quite low at pH 6.0. Similar rank-order correlations were found when ether or carbon tetrachloride was substituted for heptane. As expected for these weakly basic alkylamine antihistamines (pKa = ~9.2), the partition coefficients increased when the pH of the phosphate buffer was increased to 7.5 (Table I).

[1] Hewlett-Packard model 5711A.
[2] Spectra-Physics Autolab Minigrator.

0022-3549/78/0700/1041$01.00/0

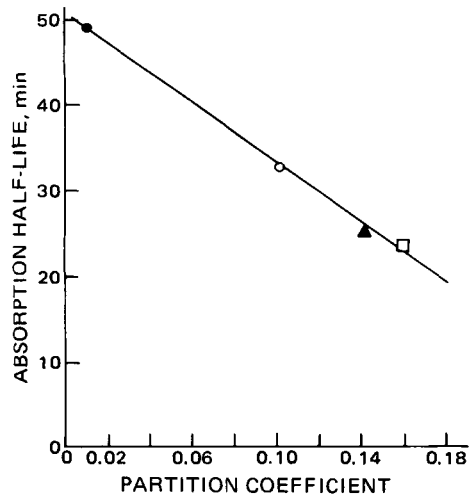

Figure 2—*Absorption half-life as a function of the heptane–phosphate buffer (pH 6.0) partition coefficient for pheniramine maleate (●), chlorpheniramine tannate (○), chlorpheniramine maleate (▲), and brompheniramine maleate (□).*

Of significance was the finding that a plot of the $t_{1/2}$ for disappearance of drug from the lumen as a function of the heptane–phosphate buffer (pH 6.0) partition coefficient was linear with a correlation coefficient of 0.998, as determined from a least-square fit to the observed data (Fig. 2). Our results are in accord with those of Schanker (3) and Kakemi *et al.* (4) who found an excellent correlation of absorption characteristics for a series of barbiturates with their corresponding lipid–water partition coefficients.

Of interest is the comparison of the absorption characteristics of these drugs to the corresponding urinary excretion data observed by Kabasakalian *et al.* (5). They found that the extent of free (unmetabolized) pheniramine excreted in the urine was greater than the extent of free chlorpheniramine excreted which, in turn, was greater than the extent of free brompheniramine excreted. Our current findings support the suggestion by Kabasakalian *et al.* (5) that the more lipid-soluble agents are to a greater extent passively reabsorbed from the kidney tubules back into the blood, allowing for further metabolism and thus resulting in decreased renal excretion of free drug. Therefore, as is true for many drugs, both absorption and excretion profiles of these alkylamine antihistamines follow patterns consistent with their overall lipid solubilities.

(1) J. T. Doluisio, N. F. Billups, L. W. Dittert, E. T. Sugita, and J. V. Swintosky, *J. Pharm. Sci.*, **58**, 1196 (1969).

(2) R. E. McMahon, *J. Med. Pharm. Chem.*, **4**, 67 (1961).

(3) L. S. Schanker, *ibid.*, **2**, 343 (1960).

(4) K. Kakemi, T. Arita, R. Hori, and R. Konishi, *Chem. Pharm. Bull.*, **15**, 1534 (1967).

(5) P. Kabasakalian, M. Taggart, and E. Townley, *J. Pharm. Sci.*, **57**, 621 (1968).

Nathan R. Strahl ˣ
Susan Lopez
College of Pharmacy
University of New Mexico
Albuquerque, NM 87131

Received March 27, 1978.
Accepted for publication April 26, 1978.
Supported in part by National Institutes of Health Grant RR 08139.

Aggregation of Dantrolene to Human Serum Albumin

Keyphrases □ Dantrolene—binding to human serum albumin, fluorescence quenching study, mechanism evaluated □ Binding—dantrolene to human serum albumin, fluorescence quenching study, mechanism evaluated □ Albumin, human serum—binding to dantrolene, fluorescence quenching study, mechanism evaluated □ Relaxants, skeletal muscle—dantrolene, binding to human serum albumin, fluorescence quenching study, mechanism evaluated

To the Editor:

A recent article (1) concerning the interaction of dantrolene, 1-[[5-(4-nitrophenyl)furfurylidine]amino]hydantoin, with human serum albumin reported difficulty saturating the protein with the drug in an aqueous system. Difference spectrophotometric titrations of these two reactants resulted in a continual hyperchromism of the complexed drug's spectral band. A saturation end-point was not reached, even though the dantrolene concentration in all test solutions was increased to its solubility limit ($\sim 1.0 \times 10^{-4}$ *M*) in the pH 7.4 buffered aqueous system. Furthermore, the albumin was not saturated even in solutions that had the protein concentration reduced 100-fold from 1.45×10^{-4} to 1.45×10^{-6} *M*.

Lack of a definite end-point in the titration was attributed to two possible causes: the poor water solubility of dantrolene, limiting the saturation of available binding sites on the albumin; or association between bound and unbound drug molecules, hindering detection of a saturation point. A closer examination of this problem indicates that the latter self-association is most likely.

The purity of dantrolene[1] as the free acid was established by TLC in three different solvent systems: acetone–chloroform (7:3), R_f 0.50; methanol–chloroform (7:3), R_f 0.55; and benzene–methanol (9:1), R_f 0.80. All solvents were the highest grade commercially available.

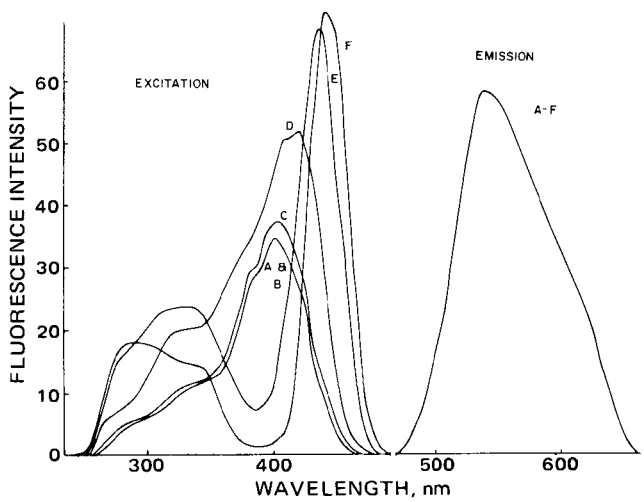

Figure 1—*Corrected fluorescence excitation and emission spectra of dantrolene in chloroform at 3.0×10^{-4} (A), 3.0×10^{-5} (B), 3.0×10^{-6} (C), 3.0×10^{-7} (D), 3.0×10^{-8} (E), and 3.0×10^{-9} (F) M. Instrumental electronic amplification was increased for each spectrum as the concentration was decreased so that the relative band shape and position of each spectrum could be seen.*

[1] Eaton Laboratories, Norwich, N.Y.

0022-3549/78/0700/1042$01.00/0