Pharmacokinetics and efficacy of chlorpheniramine in children

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Chlorpheniramine is widely used, but there is very little information about its pharmacokinetics and efficacy in children. In 11 patients with allergic rhinitis, ages 6 to 16 yr, we found a mean serum chlorpheniramine half-life of 13.1 ± 6.3 hr, a mean volume of distribution of 7.0 ± 2.8 L/kg, and a mean clearance rate of 7.2 ± 3.2 ml/min/kg. Suppression of symptoms and signs of allergic rhinitis and suppression of the histamine-induced wheal and flare responses occurred when mean serum chlorpheniramine concentrations ranged from 2.3 to 12.1 and 4.1 to 10.0 ng/ml, respectively. This, combined with the large volume of distribution for the drug, suggests that tissue binding is an important aspect of chlorpheniramine pharmacokinetics. (J ALLERGY CLIN IMMUNOL 69:376, 1982.)

Chlorpheniramine, a histamine receptor antagonist, has been used for 30 yr in the treatment of allergic rhinitis.[1] Presently, it is available in the United States in approximately 300 formulations, either alone or in combination with other drugs.[2] In addition to relieving itching, rhinorrhea, sneezing, and nasal congestion, chlorpheniramine may cause undesirable effects such as drowsiness, dryness of the mouth, and dizziness.[3, 4] Despite its widespread use, there is minimal information about its bioavailability, absorption, distribution, metabolism, and excretion in adults, and even less information about its pharmacokinetics in children. We have recently modified an HPLC assay for chlorpheniramine,[5] making it feasible to undertake pharmacokinetic studies of this drug in children. Our objectives were (1) to determine the serum t½, clearance rate, and Vd of chlorpheniramine after a single oral dose of the drug given to children with allergic rhinitis, (2) to ascertain, by means of a symptom and sign "score," the range of serum levels associated with relief of allergic rhinitis without adverse effects, and (3) to define the range of serum chlorpheniramine concentrations associated with suppression of the wheal and flare response produced by histamine in the skin.

METHODS

Patients

Chlorpheniramine was given to 11 patients with severe perennial allergic rhinitis of 6.0 ± 2.5 yr duration (mean ± SD unless otherwise specified). Their mean age was 11.0 ± 3.0 yr, and their mean weight was 39.6 ± 9.2 kg. Five had past histories of asthma or eczema for which no treatment was being given at the time of study. All had eosinophilia in blood or nasal secretions and at least two positive prick tests to common inhalant antigens. All patients had received regular chlorpheniramine treatment for at least 6 mo during the course of their rhinitis, but no patient had received it within 1 mo of study. The protocol for this investigation was approved by The Faculty Ethics Committee of the University of Manitoba, and signed informed consent was obtained from the parents and children before the study.

Procedure

Children reported to the Children's Hospital Clinical Investigation Unit at 0800 hr, fasting and having received no medications in the preceding 72 hr. They were examined, and nasal symptoms and signs and adverse effects were

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Abbreviations used
HPLC: High-pressure liquid chromatographic
t½: Elimination half-life
Vd: Apparent volume of distribution

noted (Table I). After placement of an indwelling intravenous needle and withdrawal of ~2 ml of blood, patients received a single dose (0.12 mg/kg) of commercially available chlorpheniramine maleate syrup (Chlortripolon; Schering Canada, Inc.).[4] Uniform meals and snacks were served throughout the study, beginning 2 hr after drug ingestion, and standardized activities were provided. Additional blood samples were obtained from an indwelling heparin lock 1, 3, 6, 9, 12, 15, 18, 24, and 30 hr after chlorpheniramine ingestion. Symptoms and signs of allergic rhinitis were recorded at these time intervals, and the children were questioned again about adverse effects (Table I). At 0, 6, 12, 24, and 30 hr, 0.01 ml of histamine phosphate (0.1 mg/ml) was injected intradermally on the volar surface of the forearm. A different site was utilized for each injection. The wheal and flare circumference at 10 min was traced with felt marker and transferred to the patient's record with cellophane tape. The longest diameter of each wheal and flare was measured in millimeters.

HPLC analysis of chlorpheniramine

One milliliter of test serum, or pooled serum containing standard, was pipetted into a test tube and 400 μl of internal standard solution (brompheniramine 1 μg/ml) were added. To this, 250 μl of 5% potassium hydroxide and 5 ml of ether were added. The sample was mixed for 20 sec and centrifuged for 1 min. The ether layer was transferred to a test tube containing 0.5 ml of 0.5% phosphoric acid, mixed, and centrifuged as before. The aqueous layer was frozen in a methanol/dry ice bath, and the ether layer was discarded. When the aqueous layer thawed, the sample was made alkaline with 250 μl of 5% potassium hydroxide and extracted with 5 ml of ether as before. The ether layer was transferred to a test tube and evaporated at 25° C under dry nitrogen. The sample was redissolved in 100 μl of mobile phase and injected directly into the HPLC system.

This system consisted of a U6K injector, a 6000 A High Pressure Pump, a 440 Absorbance Detector with a fixed wavelength of 254 nm, and a 7000 Data Module (Waters Associates, Inc., Milliford, Mass.). A 30 by 0.39 cm stainless steel column packed with C_{18} μ Bondpak Reverse Phase (Waters) was used. The mobile phase was 25% acetonitrile in 0.075M phosphate buffer (NaH_2PO_4), pH 2.5 (with H_3PO_4). At a flow rate of 2 ml/min the retention times were as follows: chlorpheniramine, 4.3 min; internal standard, 5 min. Drug concentrations as low as 1 ng/ml were determined. A calibration curve was constructed by plotting the peak height ratio, chlorpheniramine to internal standard, vs chlorpheniramine concentration.

Pharmacokinetic data analysis

The log of the serum chlorpheniramine concentrations were plotted against time. The terminal linear portion of the curve was fitted to the equation

$$\ln Cp = \ln Cp^0 - Kt$$

where Cp is the serum chlorpheniramine concentration any time (t), Cp^0 is the serum concentration extrapolated to zero time (t_0), and K is the first-order elimination rate constant. The t½ was calculated by the equation

$$t½ = \frac{0.693}{K}$$

Total body chlorpheniramine clearance (Cl) was calculated by the equation

$$Cl = \frac{Dose}{{}_0\int^{\infty} Cp\ dt}$$

where ${}_0\int^{\infty} Cp\ dt$ is the area under the serum chlorpheniramine concentration vs time curve calculated with the trapezoid rule, to time t_n. The area from t_n to ∞ was calculated with the equation

$${}_{t_n}\int^{\infty} Cp\ dt = \frac{Cp_n}{K}$$

The Vd was calculated with the equation

$$Vd = \frac{Cl}{K}$$

Clinical data analysis

Mean values for the symptom and sign scores and adverse effects scores were obtained by adding the values recorded at each observation time and dividing by the number of patients. The greatest wheal and flare diameters at 0, 6, 12, 24, and 30 hr were measured in millimeters and the mean values were obtained.

Pharmacokinetic[6] and clinical results were evaluated with the Student's t test.

RESULTS

Pharmacokinetics

Representative log serum chlorpheniramine concentrations vs time plots from six patients are shown in Fig. 1. The linear portions of the curve from which t½ values were calculated are designated by the solid lines. The pharmacokinetic parameters for individual patients after drug administration are shown in Table II. The mean serum chlorpheniramine t½ was 13.1 ± 6.6 hr, the mean total body clearance was 7.23 ± 3.16 ml/min/kg, and the mean Vd was 7.0 ± 2.8 L/kg. The mean peak serum chlorpheniramine concentration of 13.5 ± 3.5 ng/ml occurred at a mean time of 2.5 ± 1.5 hr.

TABLE I. Score system for symptoms, signs, and adverse effects*

Symptoms and signs		Adverse effects	
Symptoms		Sleepiness†	
Nose: Congestion		Faintness	
Itching		Dryness of the mouth	
Need to blow		Shakiness	
Discharge		Dizziness	
Eyes: Itching		Excitement	
Tearing		Headaches	
		Incoordination	
		Diplopia	
Signs		Blurred vision	
Nose: Rhinorrhea		Tinnitus	
Edema		Nervousness	
Patient rubbing nose		Frequency	
Eyes: Conjunctival erythema		Anorexia	
Lacrimation		Nausea	
		Vomiting	
		Epigastric distress	

*Symptoms and signs were scored separately from adverse effects. Scoring system: 0 = none; 1 = mild—report of symptom elicited by direct questioning and child does not complain spontaneously; 2 = moderate—child complains of symptom only once spontaneously and is still actively involved in the activities of the unit; 3 = severe—child complains more than once of symptoms but still takes part in activities; 4 = intolerable—child appears obviously ill.
†Omitted from scoring system between 15 and 24 hr.

TABLE II. Pharmacokinetic parameters calculated for children after an oral dose of 0.12 mg/kg chlorpheniramine maleate

Patient No.	Sex	Age (yr)	Weight (kg)	K (hr^{-1})	t½ (hr)	AUC (ng/ml/hr)	Cl (ml/min/kg)	Vd (L/kg)	Peak concentration (ng/ml)	Peak time (hr)
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		10.95	39.63	0.07	13.1	246.16	7.23	7.0	13.5	2.5
±SD		±2.98	±9.19	±.03	±6.6	±125.42	±3.16	±2.8	±3.5	±1.5

AUC = area under the curve.

Biologic effects

Significant suppression ($p \leq 0.05$) of mean symptom and sign scores occurred throughout the study (Fig. 2), when mean serum chlorpheniramine concentrations ranged from 2.3 to 12.1 ng/ml. Significant suppression ($p \leq 0.05$) of mean greatest wheal and flare diameter occurred up to and including 24 hr over a mean serum chlorpheniramine concentration range of 4.1 to 10.0 ng/ml (Fig. 3.).

Before chlorpheniramine administration, five children reported nervousness, excitement, dry mouth, or nausea. These mild symptoms were probably related

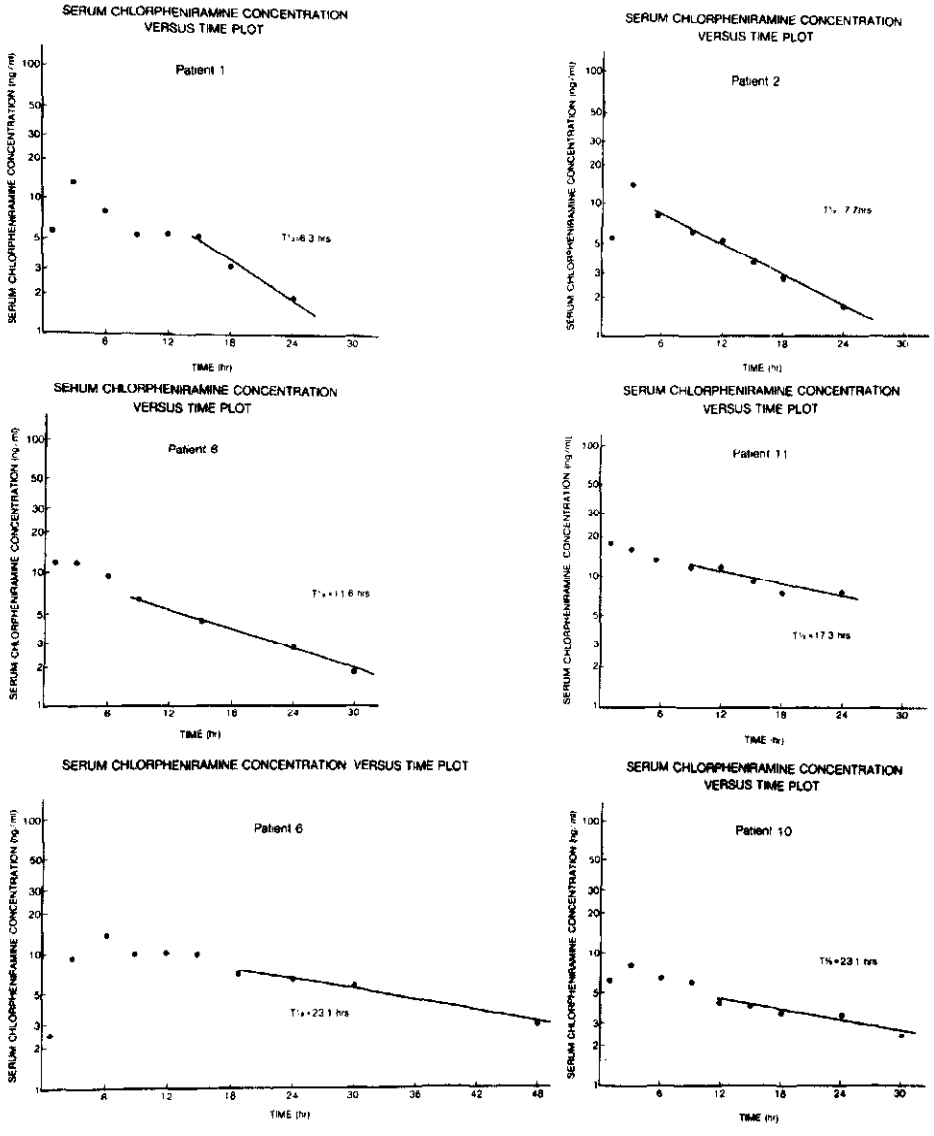

FIG. 1. Serum chlorpheniramine concentration vs time plots in six representative patients.

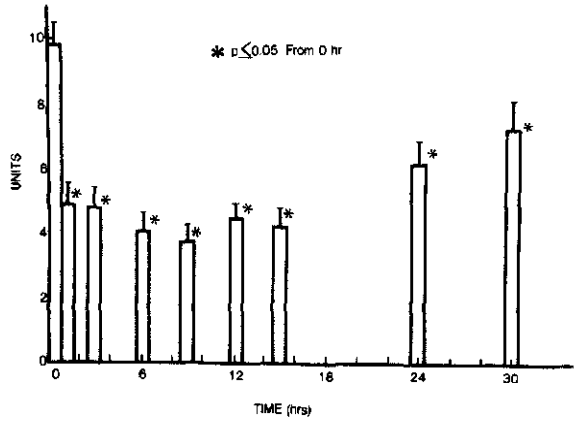

FIG. 2. Mean clinical scores + SEM in 11 children before and at 1, 3, 6, 9, 12, 15, 24, and 30 hr after chlorpheniramine ingestion.

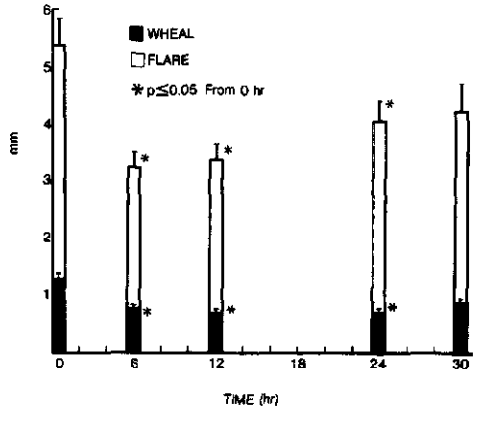

FIG. 3. Mean wheal and flare sizes + SEM in 11 children before and at 6, 12, 24, and 30 hr after chlorpheniramine ingestion.

to the child's anxiety about the study or to fasting. Ten children had one or more mild complaints of sleepiness, dry mouth, excitement, or nausea at 1 and/or 3 hr after drug administration. The sleepiness was probably a true side effect, since school-age children are unlikely to be sleepy before noon. After 3 hr few children had any symptoms that could be attributed to chlorpheniramine. The mean score for adverse effects did not differ significantly at 1, 3, 6, 9, and 30 hr from the prestudy score.

DISCUSSION

Pharmacokinetic studies

The pharmacokinetic data obtained in this study in 11 children were similar to data obtained in a 12-yr-old child given chlorpheniramine by the intravenous route.[7] We found a mean chlorpheniramine elimination rate constant of 0.07 ± 0.03 hr^{-1} and a mean t½ value of 13.1 ± 6 hr, similar to values of 0.04 hr^{-1} and 15.6 hr reported in the single patient previously studied by others. The mean clearance rate was 7.2 ± 3.2 ml/min/kg, and the mean Vd was 7.0 ± 2.8 L/kg in our patients. In the child previously studied, the clearance rate was 5.92 ml/min/kg and the Vd was 8.0 L/kg.[7]

In adults, a wide range of chlorpheniramine pharmacokinetic values has been documented. Mean t½ values of 24.4 ± 6 hr,[8] 21.0 ± 4.9 hr,[9] and 28.0 (range 19 to 43) hr[10] were significantly longer ($p \leq 0.05$) than values of 13.1 ± 6.6 hr obtained in the children in this study. Mean clearance rates of 4.4 ± 1.4 ml/min/kg for adults obtained in one study[9] were significantly lower ($p \leq 0.05$) than values of 7.23 ± 3.2 ml/min/kg obtained in this study in children, although values of 7.92 ± 1.8 ml/min/kg obtained in adults in another study[8] were not significantly different ($p = 0.05$). In the latter study,[8] the drug was administered intravenously, and there was wide scatter in the serum chlorpheniramine concentration vs time plots. The clearance rate for chlorpheniramine in children appears to be significantly faster than it is in adults. Because chlorpheniramine is extensively metabolized,[11] a reduction in metabolic enzyme activity with age could be the explanation for this. In our patients, there was no correlation of clearance rates with age ($r = 0.25$) because of the wide interpatient variability in clearance rates.

In adults, mean Vd values reported previously are 5.9 ± 0.9 L/kg[8] and 7.7 ± 2.1 L/kg,[9] which do not differ significantly ($p = 0.05$) from the mean value of 7.0 ± 2.8 L/kg found in the children in our study. The extremely large Vd values, larger than any physiologic volume, suggest extensive tissue binding of chlorpheniramine. Suppression of the signs and symptoms of rhinitis and suppression of the wheal and flare responses observed when serum chlorpheniramine concentrations are negligible also indicate extensive tissue distribution.

Biologic effects

The true duration of action of chlorpheniramine in children is unknown but is usually stated to be 4 to 6 hr.[3, 4] In the present study, in which no placebo control was used, signs and symptoms of allergic rhinitis were significantly suppressed up to and including 30 hr after administration of one dose of chlorpheniramine. The significant suppression of mean greatest wheal and flare diameters, which occurred up to and including 24 hr, was not surprising, since an earlier double-blind study revealed that 4 mg of chlorpheniramine four times daily for 3 days suppressed immediate skin-test responses for about 2.5 days after the last dose.[12]

There was an inverse correlation between mean serum chlorpheniramine concentrations at each observation time and mean symptom and sign scores obtained ($r = 0.75$). There was also an inverse correlation of mean serum chlorpheniramine concentrations with mean wheal and flare diameters ($r = 0.68$ and $r = 0.92$, respectively).

The children experienced only mild transient side effects from chlorpheniramine over a serum concentration range of 5.5 to 18.5 ng/ml. Lack of toxicity may have occurred because they all had received chlorpheniramine treatment before the study and had possibly developed some tolerance to its adverse effects[3, 4] or because chlorpheniramine has a low incidence of side effects compared with other antihistamines.[12] In view of the large numbers of patients who receive the drug with conspicuous lack of serious adverse effects, widespread monitoring of serum chlorpheniramine concentrations will not be necessary. However, monitoring may be useful in certain situations, e.g., in assessing patient compliance and in differentiating patients who do not respond to chlorpheniramine from those who do not absorb the drug optimally.

Further double-blind investigations of the relationship between the antihistaminic effects of chlorpheniramine and serum and tissue chlorpheniramine concentrations are indicated. The mean serum t½ of chlorpheniramine in children is about 13 hr, but even when serum chlorpheniramine concentrations are low, effective tissue concentrations may still be present. We speculate that the conventional practice of administering chlorpheniramine three or four times daily[3, 4] is unnecessarily frequent in many children.

We acknowledge the skilled technical assistance of Mrs. E. Frith in performing the chlorpheniramine assay. The chlorpheniramine standard was a gift from Schering Canada, Inc., and the brompheniramine internal standard was a gift from A. H. Robins Canada, Ltd.

Note added in proof

Thompson JA, Bloedow DC, and Leffert FH (J Pharm Sci **70**:1284, 1981) report a mean chlorpheniramine t½ of 9.6 ± SD 3.6 hr and a mean clearance rate of 327 ± 87 ml/hr/kg after a single intravenous dose of 0.1 mg/kg to seven children ages 6 to 14 yr. These values are not significantly different from the values reported in our article ($p = 0.05$).

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