Pharmacokinetics of Intravenous Chlorpheniramine in Children

JOHN A. THOMPSON *x, DUANE C. BLOEDOW *, and FRED H. LEFFERT ‡§

Received January 30, 1981, from the *School of Pharmacy, University of Colorado, Boulder, CO 80309, and the ‡Departments of Pediatrics, National Jewish Hospital and the University of Colorado School of Medicine, Denver, CO 80206. Accepted for publication March 20, 1981. §Present address: Professional Park-on-Cleveland, 3-B Cleveland Court, Greenville, SC 29607.

Abstract □ The disposition of chlorpheniramine was examined in seven children, 6–14 years of age, following a 0.1-mg/kg iv dose. Postinjection serum chlorpheniramine levels in each subject declined biexponentially, with the greatest intersubject variability occurring in the initial distribution of the drug. The volume of distribution at steady state ranged from 1.20 to 5.46 liters/kg. The chlorpheniramine serum clearance varied approximately twofold (234–470 ml/hr/kg) and generally decreased with age. The chlorpheniramine elimination half-life in children (mean of 9.6 hr) appeared shorter than that in adults, probably due to higher chlorpheniramine serum clearance in children.

Keyphrases □ Chlorpheniramine maleate—pharmacokinetics of intravenous drug in children □ Pharmacokinetics—intravenous chlorpheniramine maleate in children □ Antihistaminics—pharmacokinetics of intravenous chlorpheniramine maleate in children

Antihistamines represent a primary pharmacological approach to therapy for conditions such as allergic rhinitis and urticaria in patients of all ages. An appropriate antihistamine and its dose are often chosen by trial and error, sometimes with marginal success. Failure of an antihistamine to provide adequate relief could be due to intrinsic limitations in the drug's effectiveness or to suboptimal dosing due to a lack of pharmacokinetic information.

Although chlorpheniramine maleate has been a widely used antihistamine for many years, only limited pharmacokinetic information on it has been reported, and no information for children is available. Studies with adults reveal inconsistencies in biological half-life, with values ranging from 2 to 43 hr. (Table I) (1–7). Recently reported longer half-lives for chlorphreniramine have been attributed to longer blood sampling periods (6).

A highly sensitive assay procedure for chlorpheniramine was recently developed (8). The distribution and elimination of chlorpheniramine following intravenous administration of the drug to children were examined using this technique. This report presents the results of these studies.

EXPERIMENTAL

Methods—Seven children, 6–14 years of age and 24–63 kg (Table II), were studied. The children were participating in a study of chronic rhinitis, and all had perennial rhinitis but no other significant medical problems. None had received antihistamines or any other medication for at least 1 month prior to the study. The children were studied for a 24-hr period[1].

Chlorpheniramine maleate[2], 0.10 mg/kg, was administered intravenously over 5 min by an infusion pump[3]. Serum was obtained from venous blood samples collected immediately prior to drug administration and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hr following completion of the 5-min infusion. Serum was stored at −70° until analyzed.

Chlorpheniramine analysis was performed by GLC–mass spectrometry. A tetradeuterated analog was prepared for use as the internal standard. Each serum sample (2.0 ml) was mixed with 85 ng of the internal standard, and extractions were carried out as previously described[4] (8). Final extracts were evaporated to dryness, redissolved in 5 μl of acetonitrile, and analyzed[5]. Ion current was monitored for m/z 203 (chlorpheniramine) and 207 (tetradeuterated chlorpheniramine). Peak area ratios were converted to concentrations by using a calibration curve for the chlorpheniramine concentration range of 0–160 ng/ml.

Table I—Summary of Available Information on Chlorpheniramine Half-Life in Adults

Half-Life, hr	Number of Subjects	Dose, mg	Route	Blood-Sampling Period, hr	Reference
2[a]	6	4	Oral tablet	5	1
12–15	6	12	Oral tablets	48	2
28	2	4	Intravenous	48	2
4	3	4	Oral syrup	12	3
24.5–36.3	4	8	Oral capsule	48	4
18	4	4,8,12	Oral	24	5
19–43	5	8	Oral tablet	60	6, 7
22, 23	2	5	Intravenous	60	6, 7

[a] Estimated from Ref.

The serum chlorpheniramine concentration (C) *versus* time curve for each subject was computer-fitted[6] (9) to the biexponential equation:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

where A, α, B, and β are constants. Coefficients of determination (r^2) ranged from 0.991 to 1.000, and correlation coefficients (r) ranged from 0.989 to 0.997, indicating that the biexponential equation adequately describes the time course of serum chlorpheniramine concentrations after short-term intravenous infusion.

Following correction of A and B for the 5-min injection period, the intercepts (A and B) and slopes (α and β) were used to calculate the distribution of half-life ($t_{1/2,\alpha}$), the biological half-life ($t_{1/2,\beta}$), the initial dilution volume (V_1), the volume of distribution at steady state (V_{ss}), the postdistribution volume (V_β), and the serum clearance (Cl) (10).

RESULTS

The biexponential decline of serum chlorpheniramine in a representative child (Subject SW) is shown in Fig. 1. Pharmacokinetic parameters describing chlorpheniramine distribution and elimination in this group of children are summarized in Table II. In this small group, no significant correlations could be shown relating absolute (not weight-adjusted) distribution volumes or serum clearance to total body surface area (11) (V_1, $r = -0.399$; V_{ss}, $r = 0.467$; V_β, $r = 0.619$; and Cl, $r = 0.638$). Similarly, correlations relating absolute distribution volumes or clearance to total body weight were not significant(V_1, $r = -0.394$; V_{ss}, $r = 0.511$; V_β, $r = 0.654$; and Cl, $r = 0.695$). The distribution volumes and clearance values in Table II have been weight adjusted to facilitate comparison to available literature data for chlorpheniramine disposition in adults.

The initial distribution of the drug was quite variable, as evidenced by a large intersubject variation in the initial dilution volume (V_1), α, and $t_{1/2,\alpha}$. The intersubject variability of other pharmacokinetic parameters is in the range given for other drugs in children (12).

[1] Clinical Research Unit, National Jewish Hospital, Denver, Colo.
[2] Schering Corp., Kenilworth, N.J.
[3] Harvard Apparatus Co., Millis, Mass.

[4] *Erratum*—In Reference 8, the following corrections should be made. On page 708, column 1, the next to last line should read "a 0.10-mg/kg dose." On page 709, column 1, Table II, should read: Initial dilution volume (V_c), 2.982 liters/kg; Volume of distribution during postdistribution phase (V_β), 5.628 liters/kg; total body clearance 4.15 ml/min/kg. On page 709, column 2, line 6 should read "intravenous dose of 0.10 mg/kg."
[5] Model 5984A, Hewlett-Packard, Palo Alto, Calif.
[6] CDC 6400 computer.

0022-3549/81/1100-1284$01.00/0

Table II—Pharmacokinetic Parameters in Children following a 0.1-mg/kg iv Dose of Chlorpheniramine Maleate

Subject	Age, yr	Height, cm	Weight, kg	Surface Area,[a] m^2	α, hr^{-1}	$t_{1/2,\alpha}$, hr	β, hr^{-1}	$t_{1/2,\beta}$, hr	V_1, liters/kg	V_{ss}, liters/kg	V_β, liters/kg	Cl, ml/hr/kg
TM	6	122	24	0.903	1.78	0.39	0.0796	8.7	1.93	4.79	5.19	413
SB	9	137	28	1.05	3.89	0.18	0.0794	8.7	1.35	3.80	3.96	314
CG	9	142	37	1.21	1.25	0.55	0.0857	8.1	1.87	4.76	5.49	470
MP	11	155	38	1.31	4.13	0.17	0.133	5.2	0.145	1.20	2.28	302
TB	12	147	33	1.18	1.31	0.53	0.0443	15.7	2.98	5.46	5.63	249
SW	14	165	57	1.62	4.38	0.16	0.0526	13.2	0.537	4.06	4.45	234
MR	14	165	63	1.69	4.41	0.16	0.0904	7.7	0.352	2.62	3.12	282
Mean		148	40	1.28	3.02	0.31	0.0807	9.6	1.31	3.81	4.30	323
±*SD*		15	15	0.29	1.49	0.18	0.0288	3.6	1.03	1.46	1.26	87
CV, %		10	38	23	49	58	36	38	79	38	29	27

[a] Estimated using the equation (11): surface area (m^2) = weight $(kg)^{0.425}$ × height $(cm)^{0.727}$ × 0.007184.

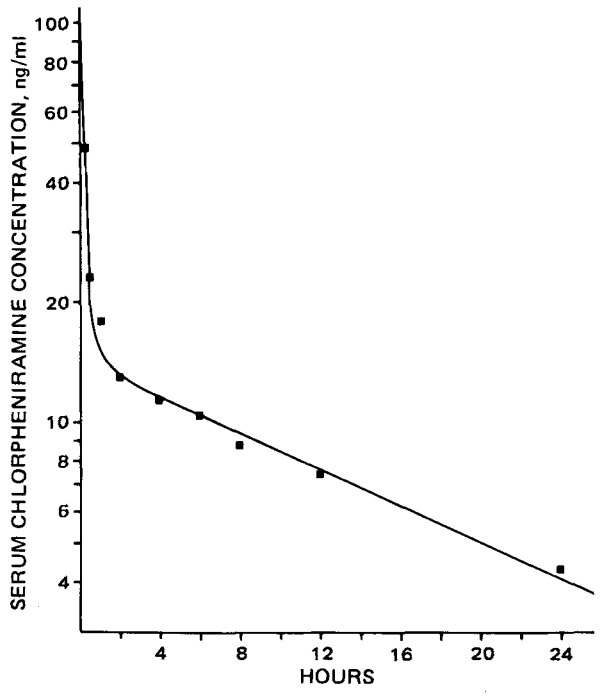

Figure 1—*Serum chlorpheniramine concentrations following the intravenous administration of a 0.1-mg/kg dose of chlorpheniramine maleate to Subject SW.*

DISCUSSION

The biological half-life for chlorpheniramine in adults has been reported to be as short as 2 hr and as long as 43 hr (Table I). Recent adult studies used a sensitive liquid chromatographic method to show that the chlorpheniramine half-life was 22 and 23 hr following intravenous administration to two subjects and 19–43 hr following oral administration to five subjects (6, 7). The previously reported shorter half-lives for chlorpheniramine in adults could be attributed to shorter blood sampling periods (6) and assay differences. A comparison of the biological half-lives for chlorpheniramine in this group of children (5.2–15.7 hr, Table II) with biological half-lives reported recently for adults indicates that the drug is eliminated much more rapidly from children than from adults.

Biological half-life ($t_{1/2,\beta}$) is directly related to (V_β) and inversely related to Cl according to:

$$t_{1/2,\beta} = \frac{0.693 \cdot V_\beta}{Cl} \qquad \text{(Eq. 2)}$$

Comparisons between recently reported adult data and the data from this study in children offer evidence that the shorter chlorpheniramine biological half-life in children is primarily due to a greater chlorpheniramine serum clearance in children rather than to a difference in distribution volumes. The chlorpheniramine postdistribution volume (V_β) in children averaged 4.30 liters/kg (range 2.28–5.63 liters/kg) and is similar to the postdistribution volume reported for adults (7) (3.2 and 3.6 liters/kg). The serum clearance for chlorpheniramine in children averaged 323 ml/hr/kg (range 234–470 ml/hr/kg), while plasma clearance in adults is ~100 ml/hr/kg (estimated from Ref. 7). The more rapid elimination of chlorpheniramine from children compared to adults is similar to that reported for other drugs (13). Interestingly, in this small sample of children the serum clearance of chlorpheniramine is negatively correlated with age ($r = -0.799$, $p < 0.05$) and, no correlation could be shown between serum clearance and weight ($r = -0.144$) or body surface area ($r = -0.551$).

Presently available information is insufficient for formulation of dosing recommendations for children; data on the relation between serum chlorpheniramine level and biological effect are needed. Little is known about the optimum chlorpheniramine serum concentration necessary for treatment of the clinical conditions for which the drug is used. In addition, since chlorpheniramine is commonly administered orally, an estimate of bioavailability would be necessary for formulating dosing recommendations. Studies in adults indicated that oral bioavailability is low (25 and 44% in two subjects following administration of tablets), possibly due to an extensive gut first-pass effect (7). Oral chlorpheniramine bioavailability estimates have not been reported for children.

Although optimum serum chlorpheniramine levels and bioavailability in children have not been reported, the apparent age-related differences in chlorpheniramine elimination indicate that adherence to a fixed milligram per kilogram maintenance dose may not be appropriate in all children. An oral dosage regimen of 0.35 mg/kg/day in four doses (or 0.0875 mg/kg every 6 hr) has been recommended for older infants and children (14). The desired average steady-state serum drug concentration ($\bar{C}_{ss}$) is directly related to the fraction of the oral dose absorbed (F) and the oral maintenance dose (D) and indirectly related to the serum clearance (Cl) and the dosing interval (τ) according to:

$$\bar{C}_{ss} = \frac{F\,D}{Cl\,\tau} \qquad \text{(Eq. 3)}$$

With the assumption of no variation in bioavailability (F), the recommended oral dosage regimen could produce a twofold variation in average serum levels ($\bar{C}_{ss}$), based on the twofold variation in the chlorpheniramine serum clearance in the group of children studied (Table II). The data suggest that younger children may require a slightly larger milligram per kilogram dose than the older child to produce equivalent serum chlorpheniramine levels, barring age-related differences in bioavailability.

Based purely on pharmacokinetic considerations, frequent dosing of chlorpheniramine may not be necessary in adults because of the long elimination half-life (6, 7). The present study indicates that frequent dosing may be advisable in children to reduce possible widely fluctuating and perhaps excessive or subtherapeutic serum chlorpheniramine levels. Dosing frequency decisions are complicated, however, by the generally accepted statement that the therapeutic effect of chlorpheniramine is no longer than 4 hr (2). Whether this is true in children is unclear and deserving of additional study.

REFERENCES

(1) W. E. Lange, J. M. Theodore, and F. J. Pruyn, *J. Pharm. Sci.*, **57**, 124 (1968).

(2) E. A. Peets, M. Jackson, and S. Symchowicz, *J. Pharmacol. Exp. Ther.*, **180**, 364 (1972).

(3) S. Hanna and A. Tang, *J. Pharm. Sci.*, **63**, 1954 (1974).

(4) P. Haefelfinger, *J. Chromatogr.*, **124**, 351 (1976).

(5) J. W. Barnhart and J. D. Johnson, *Anal. Chem.*, **49**, 1085

(1977).
(6) W. L. Chiou, N. K. Athanikar, and S. Huang, *N. Engl. J. Med.*, **300**, 501 (1979).
(7) S. M. Huang, N. K. Athanikar, K. Sridhar, Y. C. Huang, and W. L. Chiou, "Abstracts," vol. 8, no. 2, APhA Academy of Pharmaceutical Sciences, 1980, p. 82.
(8) J. A. Thompson and F. H. Leffert, *J. Pharm. Sci.*, **69**, 707 (1980).
(9) C. M. Metzler, G. L. Elfring, and A. J. McEwen, *Biometrics*, **30**, 562 (1974).
(10) M. Gibaldi and D. Perrier, "Pharmacokinetics," Dekker, New York, N.Y., 1975, pp. 48, 68, 177.
(11) D. DuBois and E. F. DuBois, *Arch. Intern. Med.*, **17**, 863 (1916).
(12) E. F. Ellis, R. Koysooko, and G. Levy, *Pediatrics*, **58**, 542 (1976).
(13) A. Rane and J. T. Wilson, *Clin. Pharmacokinet.*, **1**, 2 (1976).
(14) H. C. Shirkey, "Pediatric Clinical Pharmacology and Therapeutics in Drug Treatment," Adis Press, New York, N.Y., 1980, p. 126.

ACKNOWLEDGMENTS

Partially supported by the Council for Research and Creative Work of the University of Colorado.

The authors thank Mr. John Ivy for assistance with the serum extractions.

Application of One-Phase End-Point Change System in Two-Phase Titration to Amine Drug Analysis

MASAHIRO TSUBOUCHI *x, **HIROMI MITSUSHIO** ‡, **NAKAMICHI YAMASAKI** ‡, and **KIYOSHI MATSUOKA** ‡

Received December 2, 1980, from the *Laboratory of Chemistry, Kochi Medical School, Oko, Nankoku, Kochi 781-51, Japan, and the ‡ Department of Geology, Faculty of Science, Kochi University, Asakura, Japan. Accepted for publication March 30, 1981.

Abstract □ A titration method was developed for the determination of diphenhydramine, quinine, neostigmine, sparteine, strychnine, homatropine, atropine, physostigmine, and procaine in aqueous solution. Tetraphenylborate was used as a titrant with tetrabromophenolphthalein ethyl ester as an indicator in the presence of organic solvent. End-point detection was based on the color change of the indicator in the organic phase without movement of the indicator from one phase to the other.

Keyphrases □ Amine drugs—analysis, two-phase titration □ One-phase end-point change system—two-phase titration, amine drugs □ Two-phase titration—amine drugs, one-phase end-point change system

Titration methods permit the convenient determination of organic and inorganic ions without complex instrumentation. Solvent extraction techniques are also convenient in the titration field. Two-phase titration (ion-pair extraction–titration) using methylene blue was proposed by Weatherburn (1) in 1950. However, with this two-phase dye transfer titration method, it is generally difficult to detect the end-point because a dye color in an aqueous layer reflects to the organic layer (2). Subsequently, additional reports (2–5) described two-phase dye transfer procedures involving modifications of the methylene blue method and substitutions of various dyes for methylene blue.

Titration end-point detection, however, can be a problem with the two-phase titration method due to color reflectance between phases and differences in the color shade or hue in the two phases. These problems occur because the end-point detection in the two-phase titrations is based on the transfer of the indicator dye from one phase to the other, with end-points usually taken when color intensity is judged to be equal between the two phases. The two-phase titration has been applied only to the determination of surfactants. Mohammed and Cantwell (6) recently developed a two-phase photometric titration method for the determination of drugs and surfactants.

The present paper reports a new two-phase titration method based on the change of indicator in only one phase without movement of the indicator from one phase to the other. This one-phase end-point change system provided the two-phase titration method for the determination of amines in aqueous solution. Colorimetric and nonaqueous titrimetric methods were used for the determination of alkaloids or amines.

EXPERIMENTAL[1]

Reagents—The potassium salt of tetrabromophenolphthalein ethyl ester, dissolved in ethanol to make a 0.1% solution, was used as the indicator.

Buffer Solution—A borate–phosphate buffer was prepared by adding 2 *N* H_2SO_4 to a 0.2 *M* dibasic sodium phosphate solution containing 0.1 *M* sodium borate.

Titrant—Sodium tetraphenylborate (3.422 g), dried at 80°, was dissolved in water and diluted to 1 liter to make a 0.01 *M* solution.

Amine Solution—Sample solutions of diphenhydramine, quinine, neostigmine, sparteine, strychnine, atropine, physostigmine, and procaine were prepared by dissolving their hydrochlorides, bromides, or sulfates in 0.002 *N* H_2SO_4. The solutions were standardized by the official method (7).

Titration Procedure—The proposed titration methods with a one-phase end-point change system are summarized in Table I. For example, the determination of diphenhydramine was as follows: 1–10 ml of diphenhydramine solution (0.01 or 0.005 *M*), 5 ml of borate–phosphate buffer (pH 5.5–7.5), 10 ml of ethylene dichloride, and 3–4 drops of indicator solution were placed in a 300-ml erlenmeyer flask. The mixture was titrated with 0.01 *M* tetraphenylborate solution with manual intermittent shaking to ensure equilibrium between the organic solvent and the aqueous phase.

The other amines or alkaloids in Table I were treated in the same manner as described for diphenhydramine.

RESULTS AND DISCUSSION

End-Point Color—The one-phase end-point change system is based on the hydrophobic indicator, which is able to react with ions in the aqueous phase. The tetrabromophenolphthalein ethyl ester indicator is a monoprotic acid and can form ion associates or charge transfer complexes with amines or alkaloids (8). The initial mixture of the amines

[1] All chemicals were reagent grade; Wako Pure Chemical Industries, Tokyo, Japan.

0022-3549/81/1100-1286$01.00/0