Comparative Pharmacokinetics of Chlorphenesin Carbamate and Methocarbamol in Man

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Abstract □ Serum drug levels following oral administration of large single doses of chlorphenesin carbamate and methocarbamol were fitted to a one-compartment open model. The appearance of each drug was described by a short lag time followed by a rapid first-order absorption and attainment of maximum levels. No statistically significant differences were found between estimates of mean lag times (t_0, 0.5 and 0.2 hr.), half-lives for absorption ($t_{1/2}$, 0.4 and 0.6 hr), and times for attainment of maximum serum concentrations (t_m, 1.9 and 1.4 hr.) for chlorphenesin carbamate and methocarbamol, respectively. Chlorphenesin carbamate was distributed throughout a significantly larger relative volume (1.27 *versus* 0.48 l./kg.) and yielded a correspondingly smaller maximum serum concentration (15.3 *versus* 29.8 mcg./ml., 2-g. dose). The mean biological half-life for chlorphenesin carbamate, 3.14 hr., was significantly greater than the value of 1.20 hr. obtained for methocarbamol.

Keyphrases □ Chlorphenesin carbamate—pharmacokinetic parameters, compared to methocarbamol, man □ Methocarbamol—pharmacokinetic parameters, compared to chlorphenesin carbamate, man □ Pharmacokinetic parameters—comparative, chlorphenesin carbamate and methocarbamol, man □ Plasma levels—comparative, chlorphenesin carbamate and methocarbamol, man

Chlorphenesin carbamate [3-(*p*-chlorophenoxy)-1,2-propanediol-1-carbamate][1] is a well-tolerated, orally active agent effective in the treatment of skeletal muscle trauma and inflammation (1–5). The pharmacology (6), metabolism (7–10), and analytical characterization (11–13) of this drug were reported. As a centrally active muscle relaxant, chlorphenesin carbamate produced a longer duration of effect than mephenesin carbamate [3-(*o*-tolyloxy)-1,2-propanediol-1-carbamate] in rats and mice (6).

Clinical estimation of duration of effect is difficult. Determination of the persistence of drug in the circulation, the resultant of rates of absorption, distribution, and elimination, provides an alternative approach assuming a correlation between biological response and circulating drug concentrations. Such a correlation was shown for structurally similar compounds in the cat (14). Accordingly, the present study was conducted to characterize the pharmacokinetics of chlorphenesin carbamate in man. Earlier investigations in man with mephenesin carbamate (15) and methocarbamol [3-(*o*-methoxyphenoxy)-1,2-propanediol-1-carbamate] (16) indicated higher and more prolonged plasma levels for the latter. However, no determination of pharmacokinetic parameters was possible from the data presented. Therefore, to permit a direct comparison with chlorphenesin carbamate, methocarbamol was included in this study.

[1] Maolate is the registered trademark of The Upjohn Co. for chlorphenesin carbamate.

Table I—Design of Comparative Study

Week	Subject: Chlorphenesin Carbamate	Subject: Methocarbamol
1	Fe, Sz	Mo, Pr
2	Ma, Mi	Br, Jo
3	Mo, Pr	Fe, Sz
4	Br, Jo	Ma, Mi

EXPERIMENTAL

Pilot Study (I)—To test the analytical method and provide preliminary data on pharmacokinetic parameters, a pilot study was conducted with chlorphenesin carbamate in two normal adult male volunteers (Re, 70.5 kg., and Mi, 90.9 kg.). Each was fasted from 6:00 p.m. of the previous day until 11:00 p.m. of the test day; a regular diet was permitted thereafter. At 8:00 a.m. of the test day, Subject Re received 3 g. and Subject Mi received 2 g. of chlorphenesin carbamate orally as 500-mg. compressed tablets. Water was consumed at the rate of 8 oz. every 2 hr. for the first 12 hr. and *ad libitum* thereafter. Serum samples were collected at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, and 24 hr. and frozen until analyzed.

Comparative Study (II)—Eight normal adult male volunteers, weighing 52.3–95.5 kg. (mean 76.5 kg.), received 2-g. oral doses of chlorphenesin carbamate and of methocarbamol as 400-mg. compressed tablets according to the schedule shown in Table I. Subjects were treated and samples were collected as in the pilot study.

Serum Analyses—Drug concentrations were determined by the following modification of the procedure of Morgan *et al.* (17). Two milliliters each of serum and 0.2 *N* sodium hydroxide were mixed in a 32-ml. glass-stoppered centrifuge tube, held 30 min. in a boiling water bath, rapidly cooled to room temperature, and vigorously shaken with 25 ml. of chloroform. Phases were separated by centrifugation for 5 min. at 2000 r.p.m., the aqueous phase was discarded, and 20 ml. of the chloroform extract was transferred to a 50-ml. round-bottom flask and carefully evaporated to dryness at atmospheric pressure in a stream of N_2. Care must be taken at this point to avoid sublimation of chlorphenesin or guaiacol glyceryl ether. One milliliter of 0.005 *M* periodic acid in 1 *M* sulfuric acid was added to the residue, oxidation was allowed to proceed for 1 hr. at room temperature, and 0.5 ml. of 0.1 *M* sodium arsenite was added. After at least 15 min., 4 ml. of chromotropic acid reagent (1.25 g. in 20 ml. of water carefully diluted to 200 ml. with 12.5 *M* sulfuric acid) was added. After thorough mixing, the solution was transferred to a glass-stoppered tube and held in a boiling water bath for 30 min.; it was then rapidly cooled.

Absorbance was determined at 570 nm. *versus* a reagent blank. Results for each subject were corrected for the pretreatment sample (serum blank) for the same subject. Calculations were based on standard curves obtained by the analysis of serum samples containing known amounts of added chlorphenesin carbamate or methocarbamol. A coefficient of variation of 5% or less was observed in the analysis of standards. Mean serum blanks were equivalent to approximately 3.5 and 2.0 mcg./ml. of chlorphenesin carbamate and methocarbamol, respectively.

Treatment of Data—Serum drug levels for each subject and each drug were fitted to a one-compartment open model, using the nonlinear least-squares program of Metzler (18) written for an IBM 360/30 computer. The pharmacokinetic parameters generated for chlorphenesin carbamate and methocarbamol were compared by the two-sided sign test (19). Subject Mo failed to exhibit measurable

Table II—Serum Drug Levels in Human Subjects following Oral Administration

	Serum Levels, mcg./ml.							
	Study I				Study II			
	Chlorphenesin Carbamate						Methocarbamol	
	Subject Re[a]		Subject Mi[b]					
Hours	Obs.	Calc.[c]	Obs.	Calc.[c]	Obs.	Calc.[c]	Obs.	Calc.[c]
1	10.2	10.5	10.7	10.6	8.3	8.3	25.8	26.2
2	19.3	19.4	17.0	17.6	14.9	14.7	25.5	23.9
3	21.4	20.2	18.1	17.5	13.3	13.7	14.5	15.4
4	17.7	18.5	17.2	15.4	12.5	11.6	8.6	8.8
5	16.4	16.2	11.5	13.0	8.8	9.5	3.5	4.8
6	13.8	14.0	9.4	10.7	7.6	7.7	4.5	2.6
8	9.8	10.2	7.7	7.2	4.9	5.1	2.2	0.7
10	7.4	7.4	4.4	4.8	3.8	3.3	—[e]	—
12	5.3	5.4	4.1	3.2	—[d]	—	—	—
15	3.7	3.3	—[d]	—	—	—	—	—

[a] 3-g. dose. [b] 2-g. dose. [c] Calculated from nonlinear least-squares fit of observed concentrations to Eq. 1. [d] Values <3.5 mcg./ml. on terminal portion were rejected. [e] Values <2.0 mcg./ml. on terminal portion were rejected.

serum drug levels following methocarbamol administration and was not included in the comparison.

RESULTS AND DISCUSSION

Analytical Method—Serum drug levels were determined by modifications of the procedure of Morgan *et al.* (17). The method involves: (*a*) alkaline hydrolysis of the carbamates in diluted serum to yield the corresponding glycols (chlorphenesin and guaiacol glyceryl ether), (*b*) chloroform extraction of the glycols, (*c*) periodate oxidation of the glycols, and (*d*) spectrophotometric determination of the resulting formaldehyde by reaction with chromotropic acid. Conditions were standardized for chlorphenesin carbamate and applied directly to methocarbamol.

Substitution of the periodic acid reagent for the bicarbonate-buffered reagent described by earlier workers (17, 20) provided greater manipulative simplicity with no increase in reaction time; oxidation of chlorphenesin was complete within 1 hr. Chloroform extraction of chlorphenesin was quantitative and unaffected by changes in the aqueous volume or the presence of serum proteins. Alkaline hydrolysis of chlorphenesin carbamate under the conditions of Morgan *et al.* (17) gave a maximum yield of chlorphenesin in simple aqueous solutions within 20 min. However, when serum was treated similarly (1 ml. plus 0.1 ml. 1 *N* sodium hydroxide), the mixture gelled during heating, making subsequent extraction impossible. Greater dilution of serum proteins at the same alkalinity (*vide supra*) provided a satisfactory system; production of chlorphenesin was maximal within 30 min. and was not affected by the presence of serum components. The overall yield was 85%, comparing favorably with the reported values of 60% for mephenesin and 80% for guaiacol glyceryl ether from mephenesin carbamate and methocarbamol, respectively (17).

Buhler (7, 8) showed that the major metabolite of chlorphenesin carbamate in man is the *O*-glucuronide; small amounts of *p*-chlorophenoxylactic acid, *p*-chlorophenoxyacetic acid, and *p*-chlorophenol were also found. Bruce *et al.* (21) recently reported that the major metabolites of methocarbamol in man are glucuronide and sulfate conjugates of the drug, 3-(*o*-hydroxyphenoxy)-1,2-propanediol-1-carbamate, and 3-(*p*-hydroxy-*o*-methoxyphenoxy)-1,2-propanediol-1-carbamate. None of these compounds responded in the present analytical procedure. The method is, therefore, specific for the drugs in the presence of their metabolites.

Pharmacokinetics—Serum levels observed for chlorphenesin carbamate in Study I (Table II) indicated that the analytical method possessed adequate sensitivity at the 2-g. oral dose, that the sampling schedule defined the appearance and disappearance of drug in the serum, and that the biological half-life was about 4 hr. Computer fitting showed these data to be consistent with a one-compartment open model such that serum drug concentration, C, at any time, t, could be calculated from:

$$C = \frac{FD}{V}\left(\frac{k}{k-K}\right)[e^{-K(t-t_0)} - e^{-k(t-t_0)}] \qquad \text{(Eq. 1)}$$

where F = fraction of the dose absorbed, D = dose, V = volume of distribution, k = first-order rate constant for absorption, K = first-order rate constant for elimination, and t_0 = lag time before absorption.

Pharmacokinetic parameters obtained from the nonlinear least-squares fit (18) of these data are shown in Table III. In addition to the constants of Eq. 1, half-lives for absorption ($t_{1/2}$) and elimination ($T_{1/2}$), maximum concentration (C_m), time of maximum concentration (t_m), and relative volume of distribution (V_r) have been included. Values for the two subjects were in good agreement. Excellent agreement between observed and calculated serum drug levels (Table II), obtained from Eq. 1 and the constants of Table III, supported the choice of the pharmacokinetic model.

Observed serum levels of chlorphenesin carbamate and methocarbamol in Study II were fitted to the same model. Representative data (Subject Mi) are shown in Table II. Results were similar to those from Study I, except for a more rapid achievement of maximum levels. With chlorphenesin carbamate, observed maximum levels occurred at 2 hr. in six subjects and at 3 hr. in one. With methocarbamol, observed maximum levels occurred at 1 hr. in four subjects, at 2 hr. in two, and at 3 hr. in one. As a consequence, estimations of the parameters of absorption (t_0, k, and $t_{1/2}$) are subject to considerable uncertainty and must be treated as approximations.

Comparative calculated pharmacokinetic parameters for the seven subjects are shown in Table IV, along with mean values and tests for significance based on the two-sided sign test. The appearance of each drug in the serum could be characterized by a short lag time followed by a rapid first-order absorption and attainment of maximum levels. No statistically significant differences were found in estimates of t_0, k, $t_{1/2}$, and t_m for the two drugs. These observations are consistent with rapid dissolution (22) and high aqueous and lipid solubilities (7, 23). Absorption from the upper intestine is indicated.

Comparisons of drug distribution provide a different picture. Highly significant differences in maximum serum concentrations (C_m) and in relative volumes of distribution (V_r) were found. Oral absorption of chlorphenesin carbamate was essentially complete; over 85% of the dose was excreted in the urine as the major metab-

Table III—Pharmacokinetic Parameters of Chlorphenesin Carbamate, Study I

Parameter[a]	Subject (Dose) Re (3 g.)	Mi (2 g.)
t_0, hr.	0.54 (0.03)	0.48 (0.07)
k, hr.$^{-1}$	1.04 (0.11)	1.04 (0.29)
K, hr.$^{-1}$	0.161 (0.011)	0.203 (0.039)
FD/V, mcg./ml.	28.7 (1.22)	26.7 (3.51)
$t_{1/2}$, hr.	0.66	0.66
t_m, hr.	2.66	2.43
C_m, mcg./ml.	20.4	18.0
$T_{1/2}$, hr.	4.30	3.42
V_r, l./kg.[b]	1.49	0.82

[a] Values in parentheses are standard deviations. [b] Maximum relative volume of distribution assuming $F = 1$.

Table IV—Comparative Pharmacokinetic Parameters

Subject	Drug[a]	t_0, hr.	k, hr.$^{-1}$	$t_{1/2}$, hr.	t_m, hr.	C_m, mcg./ml.	K, hr.$^{-1}$	$T_{1/2}$, hr.	V_r[b], l./kg.
Fe	CC	0.7	2.4	0.29	1.8	21.7	0.211	3.29	1.40
	M	0	1.0	0.67	1.2	43.3	0.764	0.91	0.38
Sz	CC	0.7	1.6	0.44	2.1	11.5	0.270	2.57	1.48
	M	0	7.9	0.09	0.3	42.8	0.667	1.04	0.46
Ma	CC	0.1	0.9	0.76	2.4	16.6	0.164	4.23	1.30
	M	0.2	0.6	1.08	2.2	26.2	0.390	1.78	0.56
Mi	CC	0.6	1.5	0.46	2.2	14.8	0.209	3.31	1.08
	M	0.2	1.2	0.58	1.3	27.4	0.673	1.03	0.38
Pr	CC	0.3	1.6	0.44	1.7	14.7	0.253	2.74	1.21
	M	0.2	1.3	0.54	1.2	22.2	0.743	0.93	0.53
Br	CC	0.4	3.2	0.22	1.3	14.6	0.196	3.54	1.19
	M	0.8	1.4	0.51	2.0	22.8	0.436	1.59	0.54
Jo	CC	0.4	1.6	0.45	1.8	13.4	0.299	2.32	1.26
	M	0.3	1.1	0.65	1.5	23.6	0.618	1.12	0.50
Mean	CC	0.5	1.8	0.44	1.9	15.3	0.229	3.14	1.27
	M	0.2	2.1	0.59	1.4	29.8	0.613	1.20	0.48
p		>0.1	>0.1	>0.1	>0.1	<0.016	<0.016	<0.016	<0.016

[a] CC = chlorphenesin carbamate, M = methocarbamol. [b] Maximum relative volume of distribution.

olite within 24 hr. Therefore, it may be concluded that the observed differences reflect extensive distribution of chlorphenesin carbamate relative to methocarbamol. A similar pattern is seen in the comparative plasma levels of mephenesin carbamate and methocarbamol reported by Huf *et al.* (16).

The mean biological half-life of 3.14 hr. for chlorphenesin carbamate was highly significantly different from the 1.20 hr. for methocarbamol. In the former case, formation of the *O*-glucuronide represents the only important route of drug elimination and is the rate-limiting process measured (7). With methocarbamol, Bruce *et al.* (21) showed that conjugates of the drug, of 3-(*o*-hydroxyphenoxy)-1,2-propanediol-1-carbamate, and of 3-(*p*-hydroxy-*o*-methoxyphenoxy)-1,2-propanediol-1-carbamate are the major metabolites excreted in human urine along with small amounts of unidentified materials. Thus, at least three simultaneous processes of metabolism (conjugation, *O*-demethylation, and hydroxylation) contribute to the shorter half-life of methocarbamol. The longer half-life for chlorphenesin carbamate is consistant with a longer duration of effect.

The one-compartment open model represents an over simplification of the actual biological system as do all models. However, this model was consistent with the data as shown in Table II, and was considered adequate for the purposes of this study. Maass *et al.* (24) recently showed that plasma levels of mephenesin in the dog can be described by the same model. Similarly, Bruce *et al.* (21) invoked this model in determining the half-life for total methocarbamol-related materials (radioactivity) in man.

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