Pharmacokinetics and Bioavailability of Pyridinol Carbamate in Humans

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Abstract □ The pharmacokinetics of two pyridinol carbamate formulations were studied after a single oral administration in 10 healthy volunteers. An open one-compartment model described the evolution of plasma concentrations as a function of time. Pyridinol carbamate was rapidly absorbed (mean lag time from 0.36 to 0.38 hr). Its elimination half-life ranged from 3.3 to 7.9 hr. The two formulations were bioequivalent.

Keyphrases □ Pyridinol carbamate—pharmacokinetics, bioavailability, comparison of two tablet formulations, humans □ Antiarteriosclerotic agents—pyridinol carbamate, pharmacokinetics, bioavailability, comparison of two tablet formulations, humans □ Anti-inflammatory agents—pyridinol carbamate, pharmacokinetics, bioavailability, comparison of two tablet formulations, humans □ Pharmacokinetics—pyridinol carbamate, humans

The human pharmacokinetics of pyridinol carbamate, a widely used antiatheromatous agent (1, 2), have been studied in only a small number of patients and with a nonspecific analytical procedure (3, 4).

In the present work, a new sensitive and specific high-pressure liquid chromatographic (HPLC) method (5) was applied to determine the pharmacokinetics and to compare the bioavailabilities of two pyridinol carbamate formulations.

EXPERIMENTAL

Subjects—After giving informed consent, 10 healthy male volunteers (25–35 years and 58–80 kg) each received, in a randomized order, a single oral 1-g dose of two different pyridinol carbamate formulations. There was a 14-day interval between the two treatments.

Treatments—The two formulations used, A[1] and B[2], were tablets containing 250 mg of pyridinol carbamate.

Protocol—One hour after a liquid breakfast, each subject received at 8:00 am four tablets of A or B with 150 ml of water. During the following 25 hr, 12 heparinized venous blood samples (5 ml) were drawn. The first standardized meal was allowed 4 hr after drug administration.

Analytical Method—Each blood sample was centrifuged within 30 min. The separated plasma was kept frozen (−80°) until assayed. Nonmetabolized pyridinol carbamate was specifically measured by using a previously described HPLC technique (5).

Calculations—The relevant pharmacokinetic parameters were computed for the two forms of pyridinol carbamate according to an open one-compartment linear model. The plot of log plasma concentrations (C, micrograms per milliliter) *versus* time (t, hours) allowed a rough determination of the absorption (k_a, hours^{-1}) and the elimination rate constants (k_e, hours^{-1}) by using the peeling method. These empirical values were used to calculate the parameters of the most probable curve:

$$C = f(t) = -Ae^{-k_{at}} + Be^{-k_{et}} \qquad \text{(Eq. 1)}$$

This calculation was achieved by an iterative program using the least-squares principle devised for a computer[3]. The lag time (T_L, hours) before the appearance of pyridinol carbamate in plasma was calculated as follows:

$$T_L = \frac{\ln A/B}{(k_a - k_e)} \qquad \text{(Eq. 2)}$$

The relative volume of distribution (V/F, liters), which is the ratio of the volume of the compartment (V) to the absolute bioavailability factor

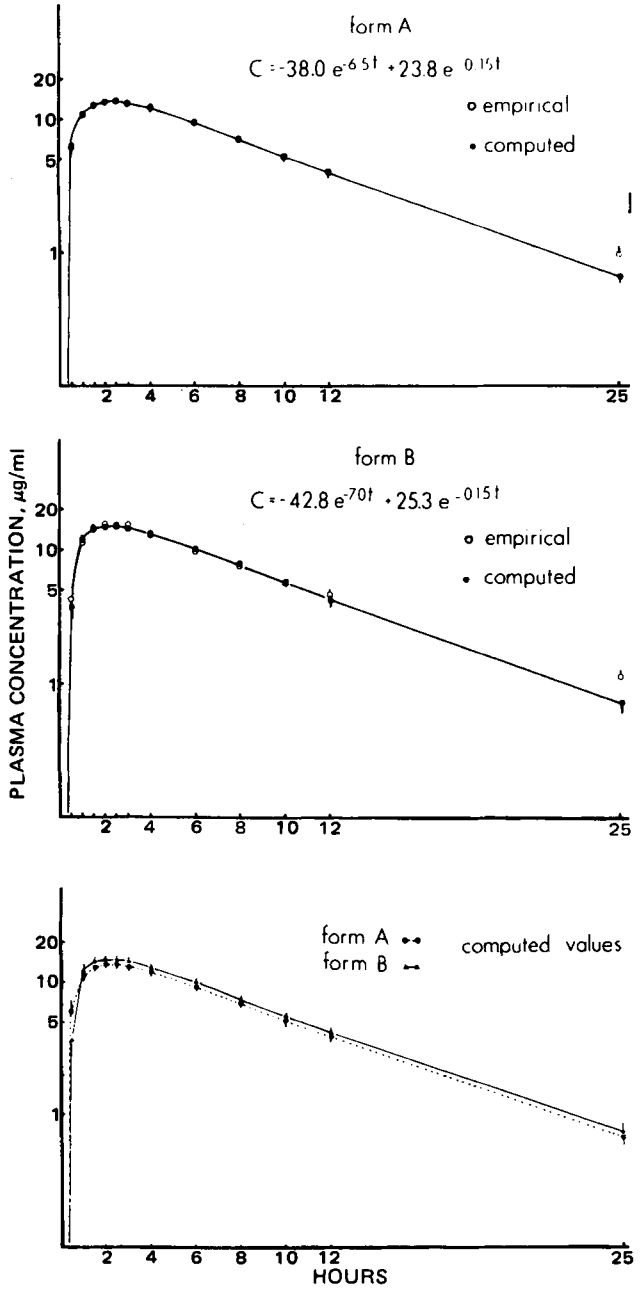

Figure 1—*Plasma concentration–time curves for pyridinol carbamate after the oral administration of 1 g of Formulations A and B in 10 healthy volunteers.*

[1] Medoxal, Allard Laboratories, Paris, France.
[2] Angioxine, Roussel Laboratories, Paris, France.
[3] Model SR 60, Texas Instruments, Almelö, Holland.

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Table I—Pharmacokinetic Parameters of Two Formulations (*A* and *B*) of Pyridinol Carbamate after a Single Oral Administration in Healthy Volunteers

Subject	Form	T_L, hr	t_{max}, hr	C_{max}, μg/ml	k_a, hr^{-1}	k_e, hr^{-1}	*A*	*B*	$t_{1/2}$, hr	$(V/F)/BW$, liters/kg	*AUC*, μg/hr/ml	AUC_{cor}, 10^{-4} μg/hr/ml	$F_{A/B}$
1	A	0.52	3.36	16.2	0.605	0.182	−53.53	42.96	3.8	0.52	149.94	1.91	1.51
	B	0.45	1.91	14.6	1.934	0.141	−46.25	20.75	4.9	0.79	127.74	1.26	
2	A	0.50	3.07	14.3	0.680	0.194	−46.38	36.45	3.5	0.73	121.63	1.37	1.23
	B	0.47	1.37	16.8	3.717	0.150	−114.38	21.50	4.6	0.90	128.22	1.11	
3	A	0.34	2.34	9.7	1.26	0.132	−21.71	14.79	5.2	1.27	95.95	0.78	0.54
	B	0.44	2.82	16.0	0.898	0.152	−41.07	9.65	4.5	0.70	152.00	1.43	
4	A	0.38	2.87	14.2	0.865	0.142	−33.79	15.73	4.8	0.73	143.49	1.36	1.04
	B	0.28	2.50	14.4	1.053	0.138	−30.45	23.54	5.0	0.76	142.05	1.31	
5	A	−0.64	1.47	15.9	1.408	0.087	−8.26	19.29	7.9	0.77	220.56	1.30	0.86
	B	0.26	1.35	19.7	3.223	0.107	−52.93	23.59	6.4	0.66	207.14	1.51	
6	A	0.36	1.09	14.0	5.025	0.145	−98.63	16 98	4.7	1.03	107.84	0.97	0.83
	B	0.50	0.61	18.6	—	0.145	−1.41	20.37	4.7	0.85	130.61	1.17	
7	A	−0.01	1.78	12.9	1.339	0.162	−19.40	19.69	4.2	0.77	107.34	1.30	0.72
	B	0.49	2.85	14.6	0.752	0.209	−48.21	36.86	3.3	0.55	114.96	1.80	
8	A	0.46	0.58	16.5	—	0.137	−1.92	18.00	5.0	0.87	122.45	1.14	0.84
	B	0.12	1.91	16.7	1.687	0.099	−26.08	21.51	7.0	0.73	202.95	1.36	
9	A	0.41	1.40	14.8	3.087	0.170	−66.26	20.01	4.0	0.71	103.68	1.41	0.90
	B	0.38	2.69	12.6	0.831	0.188	−34.78	27.20	3.6	0.64	104.05	1.56	
10	A	0.19	2.06	16.2	1.375	0.135	−30.04	23.81	5.1	0.80	154.85	1.25	0.99
	B	0.23	2.51	13.7	0.850	0.186	−32.62	28.05	3.7	0.79	113.10	1.26	
Mean	A[a]	0.38	2.00	14.5	1.738	0.149	−37.99	23.77	4.8	0.82	132.77	1.28	0.95
±*SEM*		0.06	0.29	0.6	0.477	0.010	9.23	2.87	0.4	0.06	11.69	0.09	±0.09
Mean	B[a]	0.36	2.05	15.8	1.660	0.151	−42.82	25.30	4.8	0.74	142.28	1.38	
±*SEM*		0.04	0.24	0.70	0.370	0.011	9.18	1.64	1.2	0.03	11.35	0.04	

[a] Not significant when Formulation A is compared with B.

(*F*), was obtained by using:

$$\frac{V}{F} = \left(\frac{D}{A}\right)\left(\frac{k_a}{(k_a - k_e)}\right) e^{-k_a T_L} = \left(\frac{D}{B}\right)\left(\frac{k_a}{(k_a - k_e)}\right) e^{-k_e T_L} \quad \text{(Eq. 3)}$$

where *D* is the administered dose. This parameter was corrected for body weight (*BW*, kilograms) and expressed as:

$$\frac{V}{(F)(BW)}$$

The area under the curve (*AUC*, micrograms per hour per milliliter) was calculated by integrating the equation $C = f(t)$ from $t = T_L$ to infinity:

$$AUC = -\frac{A}{k_a} e^{-k_a T_L} + \frac{B}{k_e} e^{-k_e T_L} \quad \text{(Eq. 4)}$$

This value was corrected (AUC_{cor}) for the administered dose, *BW*, and k_e relative to each subject and for the mean of these two last variables ($\overline{BW}$ and $\overline{k_e}$) for the group of volunteers as follows:

$$AUC_{cor} = AUC\left(\frac{BW}{\overline{BW}}\right)\left(\frac{k_e}{\overline{k_e}}\right) \quad \text{(Eq. 5)}$$

The plasma half-life ($t_{1/2}$, hours) was derived from k_e. The time (t_{max}, hours) needed to obtain the maximal plasma concentration (C_{max}) was obtained by:

$$t_{max} = \frac{\ln (Ak_a/Bk_e)}{(k_a - k_e)} \quad \text{(Eq. 6)}$$

The relative bioavailability factor of the two formulations ($F_{A/B}$) was calculated as follows:

$$F_{A/B} = \frac{AUC_{cor}\ \text{Form A}}{AUC_{cor}\ \text{Form B}} \quad \text{(Eq. 7)}$$

Results were expressed as means ± *SEM*. Statistical analysis of the differences between Forms A and B was carried out by a threeway analysis of variance in which the nature and the order of treatments were the two variables.

RESULTS AND DISCUSSION

The empirical and computed log plasma concentration–time curves are shown in Fig. 1, and the pharmacokinetic parameters are listed in Table I.

After oral administration, pyridinol carbamate appeared in the blood after a mean lag time of 0.36–0.38 hr. Its absorption was regular, as shown by the small interindividual variations in the plasma concentrations. No distribution phase could be detected from the plasma concentration–time curves. This finding indicates that the drug rapidly reached a relative distribution volume of 0.52–1.27 liters/kg.

Drug elimination was characterized by a plasma half-life of 3.32–7.96 hr.

These results vary with those of Mallein *et al.* (3) who reported slower absorption, higher peak plasma concentrations, and longer plasma half-lives. All of these differences could be explained by the nonspecificity of their analytical method (4) for plasma of pyridinol carbamate metabolites.

Finally, due to the absence of significant differences between the AUC_{cor} obtained after administration of the two forms and to a relative bioavailability factor ($F_{A/B}$) of 0.95 ± 0.09, it was concluded that the two pyridinol carbamate formulations were bioequivalent.

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