Kinetics and absolute bioavailability of atenolol

Twelve healthy volunteers received four single doses of atenolol (25-, 50-, and 100-mg oral solutions and a 50-mg intravenous infusion), each dose separated by at least one week. Blood and urine assayed for atenolol by a high pressure liquid chromatography (HPLC) method. Kinetic analysis of the intravenous data indicates a three-compartment model with elimination from the central compartment. The mean (± SD) terminal elimination half-life is 6.06 ± 2.02 hr, the mean volume of the central compartment is 0.173 L/kg, and 94.1 ± 8.0% of the intravenous dose is excreted in the urine. The mean value of the plasma clearance is 10.7 ± 1.27 L/hr and of the renal plasma clearance, 10.4 ± 1.14 L/hr. The mean absolute bioavailability for the 25-, 50-, and 100-mg oral doses is 0.52 ± 0.18, 0.54 ± 0.12, and 0.58 ± 0.16, respectively. The maximum plasma concentration varies as a linear function of dose. Time to mean maximum plasma concentration (3.0 hr) and the time for half of the bioavailable dose to be absorbed (2.0 hr) do not differ significantly with dose. The mean renal plasma clearance after oral doses (9.49 ± 1.6 L/hr) is in the same range as renal clearance after intravenous doses.

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Atenolol (4-2'hydroxy-3'-isopropylamino-porpoxy phenylacetamide) is a beta adrenoreceptor antagonist reported to be cardioselective and devoid of intrinsic sympathomimetic and membrane-stabilizing activity.[2, 6, 7, 8, 10] Initial clinical experience suggests that atenolol may be of value in hypertension,[9, 13, 14] that atenolol may have a sufficiently long half-life to allow once-daily dosing,[4, 7] and that absorption while consistent is incomplete. Our study was undertaken to define the kinetics and the absolute bioavailability of atenolol after intravenous and oral dosing.

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Methods and materials

Our subjects were 12 healthy adult males 21 to 28 yr of age and weighing 63.6 to 79.5 kg. Each subject was determined to be healthy on the basis of a complete physical examination, 12-lead electrocardiogram, urinalysis, hemogram, and complete blood chemistry. Each received four single doses of atenolol in an open 4-way crossover design, with 7 or more days between doses. Three doses were oral solutions (25, 50, and 100 mg) and one was a 50-mg intravenous infusion over 12 min. No food was allowed from 8 hr before dosing until 4 hr after

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Table I. *Definitions and equations*

Term	*Definitions and equations*
C_1	Postinfusion plasma concentration = $\sum_{i=1}^{n} A_i e^{-\lambda_i t^1}$
n	Number of exponentials
A_i	Pre-exponential coefficients, A_1, A_2---A_n
λ_i	Exponential coefficients, λ_1, λ_2---λ_n
t^1	Time from end of infusion = time from dose − T
T	Time of infusion
t½	Half-life of terminal exponential (λn), oral and iv
A_i'	Infusion corrected A_i, A_i', = $A_i \frac{\lambda_i T}{1 - e^{-\lambda_i T}}$
AUC(iv)	Area under the curve (0 to ∞) following the iv dose = $\sum_{i=1}^{n} A_i'/\lambda_i$
D_{iv}	Intravenous dose (50 mg)
CLP	Plasma clearance = D_{iv}/AUC(iv)
X_u^{48}	Drug accumulation in urine to 48 hr
CLR	Renal plasma clearance = X_u^{48}/AUC(iv) or X_u^{48}/AUC(po)
f	Fraction of D_{iv} excreted in urine = X_u^{48}/D_{iv}
V_1	Volume of the central kinetic compartment = $\sum_{i=1}^{n} A_i'/D_{iv}$
V_d	Area volume of distribution = D_{iv}/AUC(iv) · λn
k_{ij}	Microscopic rate constants from ith to jth compartment[15]
D_{po}	Oral dose (25, 50, 100 mg)
AUC(po)	Area under curve following oral dose (0 → ∞); trapezoid method to 24 hr plus concentration of 24 hr/λn
F_p	Fraction bioavailable from oral data = $\frac{AUC(po)}{AUC(iv)} \cdot \frac{D_{iv}}{D_{po}}$
F_u	Fraction bioavailable from urine data = X_u^{48}/D_{po} · f
$C_p$max	Maximum plasma concentration following oral dose
t max	Time from dose of Cmax
t_{50}	Time for 50% of the bioavailable dose $F_p \cdot D_{po}$ to be absorbed per Loo-Riegelman method[11]
$k_{10}^{(u)}$	Rate constant from urine data

dosing, at which time a uniform standard meal was served. During this 12-hr period, water was restricted to 240 ml, 1 hr prior to dosing, 150 ml with the dose, and 100 ml an hour until mealtime. After the meal, water was allowed ad lib and a second standard meal was served at 8 hr after the dose.

For the oral solutions, blood samples were collected before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hr thereafter. For the intravenous infusion (start of infusion at time zero) blood samples were collected at 12, 22, and 32 min and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hr. Plasma was separated immediately by centrifugation (1,764 g) and stored frozen at −30° for analysis. All urine was collected from 2 hr before dosing to 48 hr thereafter at 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48 hr. Urine creatinine was assayed as a check on urine collection and creatinine clearance. After the pH and volume for each time interval was measured, aliquots of the urine were frozen at −30° for subsequent analysis.

Plasma and urine atenolol was measured in duplicate by the HPLC method.[16] Spiked control plasma was stored with the samples and every sixth sample assayed was a control. The coefficient of variation for the assay procedure is 9% at the low range (10 ng/ml) and 5% at the high range (500 ng/ml).

Each of the 12 postinfusion plasma concentration/time curves were subjected to curve fitting using the program NONLIN[12] according to the criteria presented by Boxenbaum, Rie-

Table II. *Pharmacokinetic parameters following 50-mg intravenous infusion of atenolol*

Term	*Units*	*1*	*2*	*3*	*4*	*5*	*6*
Weight	Kg	77.3	79.1	70.5	63.6	79.1	79.6
A_1	mcg/ml	1.20 (0.08)	1.40 (0.06)	1.25 (0.13)	1.38 (0.23)	1.13 (0.05)	1.15 (0.07)
A_2	mcg/ml	0.503 (0.19)	0.333 (0.03)	0.225 (0.11)	1.16 (0.21)	0.474 (0.028)	0.370 (0.071)
A_3	mcg/ml	0.071 (0.24)	0.289 (0.125)	0.578 (0.05)	0.70 (0.03)	—	0.303 (0.08)
λ_1	hr^{-1}	3.44 (0.47)	4.63 (0.37)	4.65 (0.57)	47.5 (1,300)	2.64 (0.25)	5.21 (0.60)
λ_2	hr^{-1}	0.223 (0.11)	0.346 (0.15)	0.841 (0.57)	2.31 (0.50)	0.144 (0.01)	0.389 (0.14)
λ_3	hr^{-1}	0.059 (0.13)	0.103 (0.02)	0.145 (0.008)	0.131 (0.01)	—	0.078 (0.02)
t½	hr	11.6	6.73	4.78	5.29	4.81	8.89
AUC(iv)	mcg/ml · hr	3.98	4.27	4.73	6.20	3.88	5.24
CLP	L/hr	12.6	11.7	10.6	8.07	12.9	9.54
k_{12}	hr^{-1}	1.92	2.68	2.05	30.5	1.52	2.97
k_{21}	hr^{-1}	1.05	1.25	1.72	8.21	0.764	1.61
k_{13}	hr^{-1}	0.115	0.297	0.717	8.12	—	0.407
k_{31}	hr^{-1}	0.077	0.203	0.571	0.725	—	0.203
k_{10}	hr^{-1}	0.563	0.648	0.578	2.42	0.497	0.483
V_1	L	22.3	18.0	18.2	3.27	25.8	19.7
V_d	L	210	114	73.0	61.6	89.4	122
$k_{10}V_1$	L/hr	12.5	11.6	10.5	7.91	12.8	9.50
X_u^{48}	mg	54.0	46.9	47.3	45.6	40.6	45.9
f	—	1.08	0.937	0.946	0.912	0.813	0.919
CLR	L/hr	13.6	11.0	10.0	7.35	10.5	8.77
$k_{10}(u)(1)$	hr^{-1}	0.61	0.61	0.55	2.7	0.40	0.45
$k_{10}(u)(2)$	hr^{-1}	0.72	0.98	0.53	2.66	0.43	0.48

0. Means are computed for 11 subjects fitting three compartments when the model influences the parameter value.
1. CLR/V_1
2. Nonlinear regression $\frac{\Delta X_u}{\Delta t} = k_{10}C_i(t)\ V_1$.

gelman, and Eloshoff.[3] In this approach the weighting factor and number of exponential terms are selected on the basis of statistically ($p < 0.05$) significant reductions in the sum of squared weighted residuals and randomness of residuals. A weighting factor of $1/C_i$ was determined to be appropriate. After correction of the A_i terms for the 0.2-hr infusion period, the compartmental rate constants were computed by conventional methods.[15] Table I presents the definitions and equations employed in this report. As a check on the rate constants generated from the plasma data, the rate of appearance in the urine was evaluated. The rate of urine excretion was "fit" by NONLIN and the constant K_{10}^u determined.

A model-free approach is used for primary characterization of the plasma data following oral doses. Each of the 36 curves is characterized by a $C_p$max, t max, AUC(po), and t½ as defined in Table I. Loo and Riegelman's method,[11] modified as suggested by Wagner[15] and with interpolated values added by the method of Fried and Zeitz,[5] was used to evaluate the absorption rate and distribution into peripheral kinetic compartments.

Results

Of the 12 plasma concentration/time curves after infusion, 11 are described by a 3-exponential expression. Table II presents the parameters estimates for each subject and the asymptotic standard errors of each. The uncertainty in the first exponential is primarly due to an inadequate number of data points during the first few minutes after the infusion. The intra-

7	8	9	10	11	12	Mean	SD
75.0	79.6	77.3	68.2	64.6	75.0	74.1	5.63
1.53 (0.07)	1.39 (0.12)	0.258 (<0.001)	0.410 (0.16)	2.88 (0.05)	1.30 (0.05)	1.28	0.639
0.440 (0.057)	0.804 (0.114)	0.735 (<0.001)	1.11 (0.15)	0.334 (0.07)	0.693 (0.05)	0.610	0.303
0.393 (0.06)	0.576 (0.02)	0.573 (<0.001)	0.616 (0.02)	0.426 (0.08)	0.571 (0.01)	0.463	0.177
7.41 (0.60)	14.8 (2.9)	49.4 (13.9)	46.5 (2,400)	8.82 (0.28)	12.64 (1.1)	18.6	18.2
0.558 (0.134)	2.06 (0.32)	2.45 (0.001)	2.53 (0.37)	0.426 (0.11)	1.57 (0.14)	1.25	0.899
0.122 (0.01)	0.147 (0.005)	0.132 (<0.001)	0.136 (0.005)	0.130 (0.01)	0.151 (0.03)	0.121	0.028
5.68	4.72	5.25	5.10	5.33	4.59	6.06	2.02
4.45	4.68	4.80	5.19	4.75	4.58	4.73	0.594
11.22	10.7	10.4	9.63	10.5	10.9	10.7	1.27
4.32	6.52	27.4	25.9	5.72	6.01	10.5	10.8
1.98	5.06	19.4	17.4	1.25	4.35	5.75	6.33
0.646	3.46	3.34	3.92	0.701	2.29	2.18	2.31
0.301	0.711	0.979	0.821	0.273	0.646	0.501	0.286
0.845	1.24	0.841	1.12	1.43	1.07	1.02	0.529
13.2	8.47	12.31	8.54	7.24	10.1	12.8	5.72
92.0	72.7	78.9	70.8	80.9	72.3	95.3	40.4
11.1	10.5	10.4	9.56	10.3	10.8	10.4	1.14
48.6	49.3	49.2	52.4	45.0	39.0	47.0	4.11
0.971	0.986	0.983	1.05	0.899	0.797	0.941	0.080
10.9	10.5	10.3	10.1	9.46	8.70	10.1	1.46
0.83	1.2	0.84	1.2	1.3	0.86	0.96	0.60
1.60	1.05	0.89	1.32	1.60	0.652	1.076	0.642

venous data are consistent with a 3-compartmental model with elimination from the central compartment as shown in Fig. 1. Model parameters derived from the plasma data agree closely with the parameters derived from the urine data, with CLP and CLR and $K_{10}V_1$ being 10.7 ± 1.27, 10.1 ± 1.46, and 10.4 ± 1.14 l/hr, respectively. The rate constant for elimination, k_{10}, derived from the plasma data agrees closely with the values k^u_{10}, derived from urine data (two methods): 1.02 ± 0.53, 0.96 ± 0.60, and 1.076 ± 0.64 hr^{-1}. With the half-life of the elimination phase being 6.06 ± 2.02 hr, the 48-hr urine collection approximates closely the total drug to be excreted, and this is 94.1 ± 8.0% of the intravenous dose.

Table III presents the plasma concentration/time data following each of the 36 oral doses, and Fig. 2 is a plot of the mean plasma concentration for each of the four doses. Computations

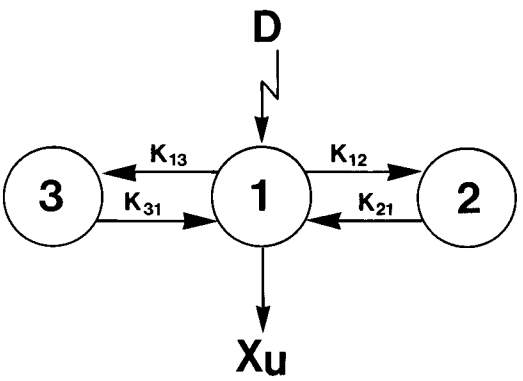

Fig. 1. Schematic for the 3-compartment model with elimination from the central compartment.

based on plasma data show the absolute bioavailability of atenolol (F_p) for the three dose levels to be 0.52 ± 0.18, 0.54 ± 0.12, and 0.58 ± 0.16 for the 25-, 50-, and 100-mg doses. The comparable values based on urine

Table III. *Pharmacokinetic parameters following oral solution of atenolol*

Parameter	*Units*	*1*	*2*	*3*	*4*	*5*	*6*
25-mg dose							
$C_p$max	mcg/ml	0.146	0.096	0.154	0.053	0.106	0.239
t max	hr	1.5	1.0	4.0	1.5	2.5	2.5
t_{50}	hr	1.25	1.25	3.00	1.25	1.75	1.50
AUC(po)	mcg/ml · hr	1.47	0.993	1.62	0.534	0.880	1.97
X_u^{48}	mg	16.8	9.7	14.6	3.1	8.6	15.2
F_p	—	0.685	0.388	0.697	0.156	0.454	0.707
F_u	—	0.622	0.414	0.617	0.136	0.423	0.662
t½	hr	9.1	8.0	8.2	5.8	6.3	6.9
CLR	L/hr	11.4	9.77	8.99	5.81	9.77	7.71
50-mg dose							
$C_p$max	mcg/ml	0.318	0.202	0.282	0.206	0.165	0.274
t max	hr	3.0	6.0	4.0	3.0	3.0	4.0
t_{50}	hr	1.25	2.75	3.00	2.50	2.00	1.75
AUC(po)	mcg/ml · hr	2.34	2.38	3.14	2.10	1.81	2.76
X_u^{48}	mg	25.3	20.1	27.6	11.2	18.1	26.1
F_p	—	0.558	0.516	0.641	0.304	0.425	0.528
F_u	—	0.469	0.429	0.584	0.246	0.446	0.568
t½	hr	8.2	7.7	6.6	9.0	8.7	6.0
CLR	L/hr	10.8	8.44	8.78	5.35	10.0	9.45
100-mg dose							
$C_p$max	mcg/ml	0.589	0.593	0.599	1.17	0.290	0.317
t max	hr	2.5	6.0	4.0	3.0	3.0	4.0
t_{50}	hr	1.25	3.75	3.50	2.00	2.50	1.50
AUC(po)	mcg/ml · hr	4.52	5.54	6.71	9.35	3.28	3.70
X_u^{48}	mg	47.6	56.3	58.3	58.5	30.7	33.9
F_p	—	0.534	0.678	0.685	0.732	0.411	0.344
F_u	—	0.441	0.600	0.616	0.641	0.378	0.369
t½	hr	4.2	2.5	7.2	6.0	11.4	8.3
CLR	L/hr	10.5	10.2	8.69	6.26	9.36	9.16

t_{50} values to nearest 0.25 hr.

data are 0.54 ± 0.19, 0.52 ± 0.15, and 0.56 ± 0.17 and agree closely with the plasma data. Thus the oral doses of atenolol are approximately 56% absorbed over the dose range studied. Another indicator of dose proportionality is the $C_p$max, which are 0.138 ± 0.058, 0.282 ± 0.088, and 0.650 ± 0.327 mcg/ml for the 25-, 50-, and 100-mg doses and are linear with dose when subjected to linear regression. There are no significant differences in the absorption rate across the three dose levels as indicated by t max and t_{50}. Examination of plots of the amount of bioavailable dose (F_p · D) remaining unabsorbed as a function of time shows a single first-order absorption rate process is not appropriate. A typical plot of the Loo-Riegelman generated curve for a subject is presented in Fig. 3. Each curve consisted of two apparent rapid first-order processes with a varying interval of relatively slow absorption between those two phases. The two rapid-absorption phases may be due to a biphasic gastric emptying pattern similar to that described by Clements and co-workers.[5] Also generated by the Loo-Riegelman computation are estimates of the amount of drug in the two peripheral compartments over time. As demonstrated in Fig. 3, the shallow compartment reaches a maximum about 1 hr after the plasma, while the deeper compartment is maximal about 2 hr after the plasma, facts which may be of value in subsequent pharmacodynamic correlations, as most of the drug is in the peripheral compartments.

Elimination following the oral doses as indi-

7	8	9	10	11	12	Mean	SD
0.136	0.084	0.053	0.207	0.197	0.185	0.138	0.058
1.5	4.0	4.0	2.0	4.0	1.5	2.5	1.1
1.25	2.75	2.25	1.50	3.00	1.50	1.85	0.673
1.19	0.992	0.700	1.76	1.58	1.78	1.29	0.449
16.6	9.7	8.2	18.0	14.9	17.1	12.7	4.5
0.464	0.381	0.286	0.676	0.630	0.716	0.520	0.183
0.683	0.394	0.333	0.687	0.661	0.857	0.541	0.192
7.7	8.3	2.8	3.8	7.2	6.0	6.7	1.8
14.0	9.78	11.7	10.3	9.41	9.63	9.85	1.93
0.291	0.226	0.207	0.436	0.318	0.462	0.282	0.088
1.5	3.0	4.0	2.5	4.0	1.0	3.3	1.3
1.50	1.75	2.75	1.75	2.25	0.75	2.0	0.63
2.32	2.00	2.42	3.49	3.37	3.64	2.65	0.594
28.9	21.2	21.3	28.6	28.3	36.2	24.4	6.18
0.505	0.403	0.550	0.674	0.705	0.717	0.544	0.121
0.595	0.430	0.433	0.547	0.628	0.907	0.524	0.153
7.3	7.0	7.3	7.3	7.4	6.2	7.4	0.87
12.5	10.6	8.82	8.19	8.40	9.95	9.27	1.68
0.263	0.592	0.382	0.769	1.05	1.19	0.650	0.327
4.0	3.0	4.0	2.0	3.0	1.5	3.3	1.12
2.50	1.75	2.00	1.50	2.25	1.00	2.13	0.810
3.30	4.96	4.34	7.08	7.58	7.76	5.68	1.90
29.5	52.9	44.2	58.4	74.0	78.6	51.9	15.0
0.321	0.527	0.484	0.642	0.814	0.783	0.580	0.160
0.304	0.537	0.449	0.557	0.821	0.985	0.557	0.174
11.1	4.5	6.5	7.6	6.2	4.7	6.7	2.6
8.95	10.7	10.2	8.25	9.76	10.1	9.34	1.18

cated by the CLR values of 9.85 ± 1.93, 9.27 ± 1.68, and 9.34 ± 1.18 L/hr and the half-lives of 6.7 ± 1.8, 7.4 ± 0.87, and 6.7 ± 2.6 hr are in such close agreement with the comparable parameters for the intravenous dose that accumulation in the urine would provide a reasonable measure of the bioavailability of atenolol.

Discussion

Atenolol is a drug whose intravenous kinetics are best described by a 3-compartment model with elimination almost exclusively by the kidney, the average renal clearance being 173 ml/min. Initial tissue distribution is very rapid, however, and for 3 subjects our study does not have sufficient data for the first few minutes to define that part of the curve. The volume of the central kinetic compartment is approximately twice the blood volume and clearance from this compartment is in close agreement with model-free clearance and renal clearance. After distribution most of the atenolol is found in the peripheral kinetic compartments.

Oral dosing over the 25-, 50-, and 100-mg range produces plasma levels directly proportional to the dose with about 56% absorption, and subsequently excretion into the urine. Although the absorption process cannot be described by a single first-order process, it is rapid enough for half of the bioavailable dose to be absorbed in approximately 2 hr with peak plasma concentration at approximately 3 hr.

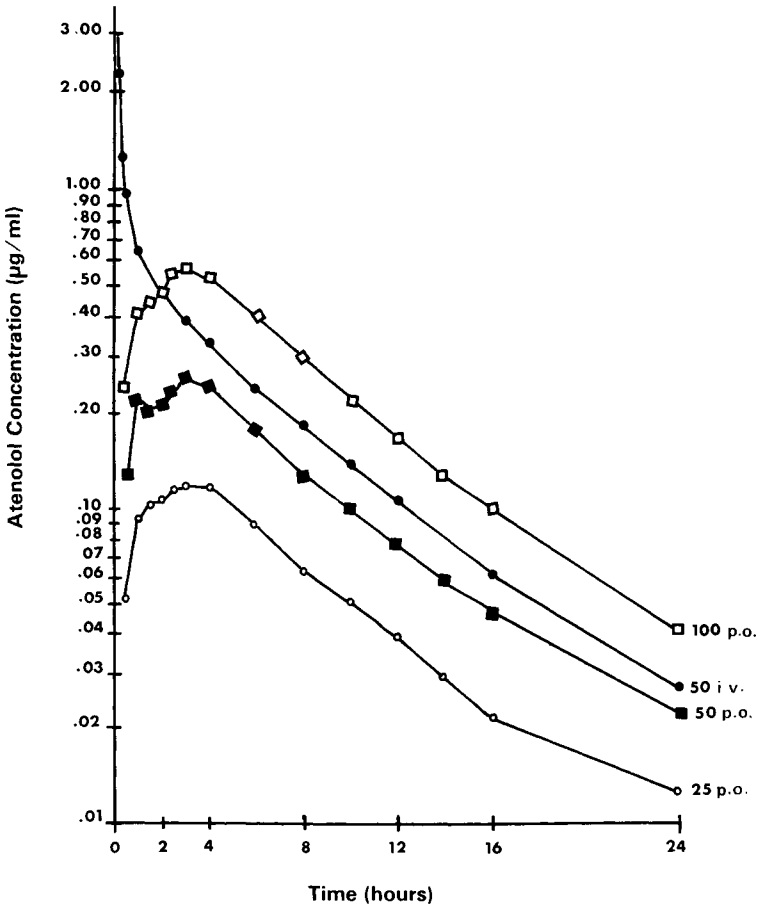

Fig. 2. Mean plasma atenolol concentration following three oral doses (25, 50, and 100 mg) and one 50-mg intravenous infusion over 12 min, for 12 normal subjects.

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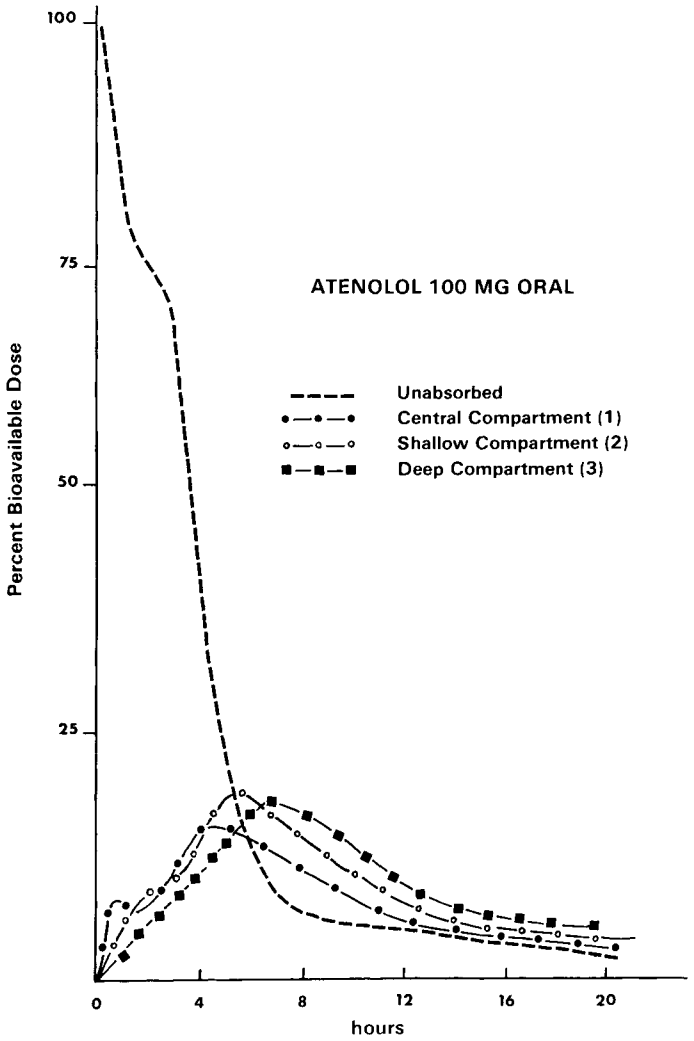

Fig. 3. Computed percent of the bioavailable dose unabsorbed and in each of the three kinetic compartments following a 100-mg dose of atenolol in one typical subject. Computed using the approach of Loo and Riegelman.[11]

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