CHAPTER IV

RESULTS AND DISCUSSION

In Vitro Studies

The five commercial brands of cimetidine tablets
were first tested for uniformity of weight and for content
of active ingredient. Each of these five brands met the
British Pharmacopoeia requirements (34) for uniformity of
weight within the range of limit weight (± 5 %). All
products were assayed for content of active ingredient.
Results indicated that each brand was within the 90-110 %
limits which met existing standard in the United State
Pharmacopoeia monograph (37) as shown in Table 2. These
data supported the assumption that all various brands
were pharmaceutically equivalent (43).

All of these five brands of cimetidine tablets
met the British Pharmacopoeia 1980 requirements for
disintegration of film-coated tablets in distilled water
at 37 ± 0.5° C within 60 minutes. Meanwhile some differences
were observed for the rates and extent of dissolution in
carbondioxide-free deionized water among the different
brands as given in Figure 2.

The mean percent drug dissolved at 15 minutes
ranged from 4.23 to 99.15 %. According to the United

State Pharmacopoeia XXI, 3rd Supplement, percent cimetidine dissolved from the tablets at 15 minutes should not less than 75 % of labeled amount. The results of this study indicated that only 3 brands (A,B and C) met the United State Pharmacopoeia specifications for drug dissolution while the other 2 brands (D and E) failed.

At 60 minutes, all products except Brand E had the mean drug dissolved over 90 %. The dissolution rate constants (k) were calculated from the slope of the first order plot between the amount of undissolved drugs $(B_\infty - B_t)$ versus time in semi-logarithmic scale (Figure 3), and the corresponding values are presented in Table 4.

According to assess the dissolution rate constants by Analysis of Variance and Student's t-test with 95 % confidence limits, there were no significant differences among Brands A, B and C. Also, the mean dissolution rate constants of these 3 brands were significantly greater than those of brands D and E ($p < 0.05$) (Appendix D).

The slower dissolution rates for Brand D and E might be due to poor solubility of film coating materials in dissolution medium. The large ranges of tablet dissolution rates of these five brands as indicated in Table 3 might be affected by compositions and methods of manufacture as well as aging of the tablets.

The disintegration and dissolution characteristics of five brands of cimetidine tablets as shown in Table 2 clearly demonstrate that there is no significant correlation between the disintegration and the corresponding dissolution for these five brands ($p > 0.05$).

Owing to the dissolution characteristics among Brands A, B and C were about the same, therefore Brand B the least retail price product, was chosen for In Vivo study to compare the bioavailability with original brand (Brand A).

Table 2   In Vitro Studies of Five Commercial Brands
of Cimetidine Tablets.

Brand	Weight[a] (mg)	Assay,%[b] of labeled amount	Disintegration[c] time (min.)	Dissolution[c] rate constant ($min.^{-1}$)	% Dissolved[c] in dissolution medium at 15 min.
A	568.25 ± 6.22	100.67 ± 0.23	2.5 ± 0.00	0.5443 ± 0.32	96.85 ± 2.61
B	538.07 ± 7.85	97.82 ± 0.43	10.0 ± 1.90	0.2858 ± 0.06	86.35 ± 4.87
C	589.99 ± 10.72	99.40 ± 0.47	7.7 ± 1.20	0.2314 ± 0.08	99.15 ± 1.78
D	545.86 ± 14.90	100.15 ± 0.31	30.7 ± 1.50	0.0502 ± 0.01	12.77 ± 6.65
E	569.47 ± 6.30	104.15 ± 0.27	11.2 ± 1.30	0.0241 ± 0.00	4.23 ± 0.60

a   =   Mean ± S.D.   (n = 20)

b   =   Mean ± S.D.   (n = 3)

c   =   Mean ± S.D.   (n = 6)

Table 3   Dissolution Profiles of Five Brands of

Cimetidine Tablets.

| Time (min)	% Drug dissolved[a]				
	Brand A	Brand B	Brand C	Brand D	Brand E
5	70.84 ± 17.07	22.73 ± 3.58	11.80 ± 4.97	0.91 ± 0.94	0.21 ± 0.02
10	94.56 ± 3.21	63.00 ± 8.79	69.70 ± 12.31	3.21 ± 1.33	1.04 ± 0.12
15	96.85 ± 2.61	86.35 ± 4.87	99.15 ± 1.78	12.77 ± 6.65	4.23 ± 0.60
20	94.95 ± 3.06	94.76 ± 1.42	96.81 ± 2.09	25.09 ± 10.38	3.97 ± 3.97
30	93.80 ± 2.45	95.91 ± 1.70	95.79 ± 2.15	46.19 ± 14.16	13.69 ± 1.25
45	90.67 ± 3.70	95.45 ± 1.96	96.81 ± 2.53	76.84 ± 9.74	20.82 ± 2.63
60	89.96 ± 2.86	97.46 ± 2.10	97.19 ± 2.66	92.04 ± 4.64	26.24 ± 3.71
90	89.92 ± 2.92	97.02 ± 1.85	93.79 ± 1.69	98.74 ± 2.70	35.05 ± 4.81
120	92.24 ± 2.91	96.41 ± 2.00	94.66 ± 1.95	98.89 ± 2.92	40.25 ± 5.69

a   Mean ± S.D. (n = 6)
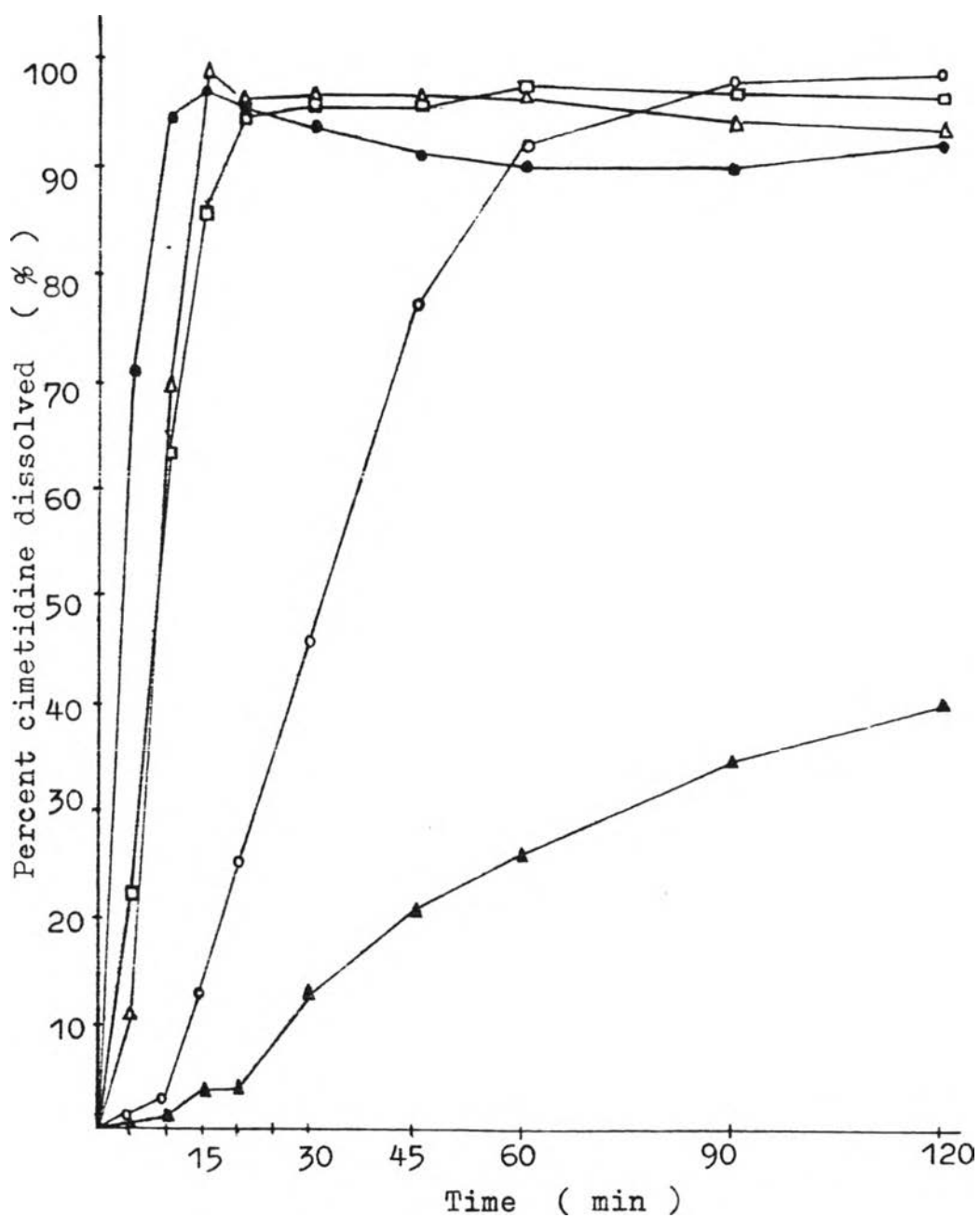
Figure 2 Dissolution profiles of five brands of
cimetidine tablets in carbondioxide-free
deionized water.

Key : Brand A (●), Brand B (□),
       Brand C (△), Brand D (o),
       Brand E (▲).

Table 4   Dissolution Rate Constant (k) for Five

Brands of Cimetidine Tablets.

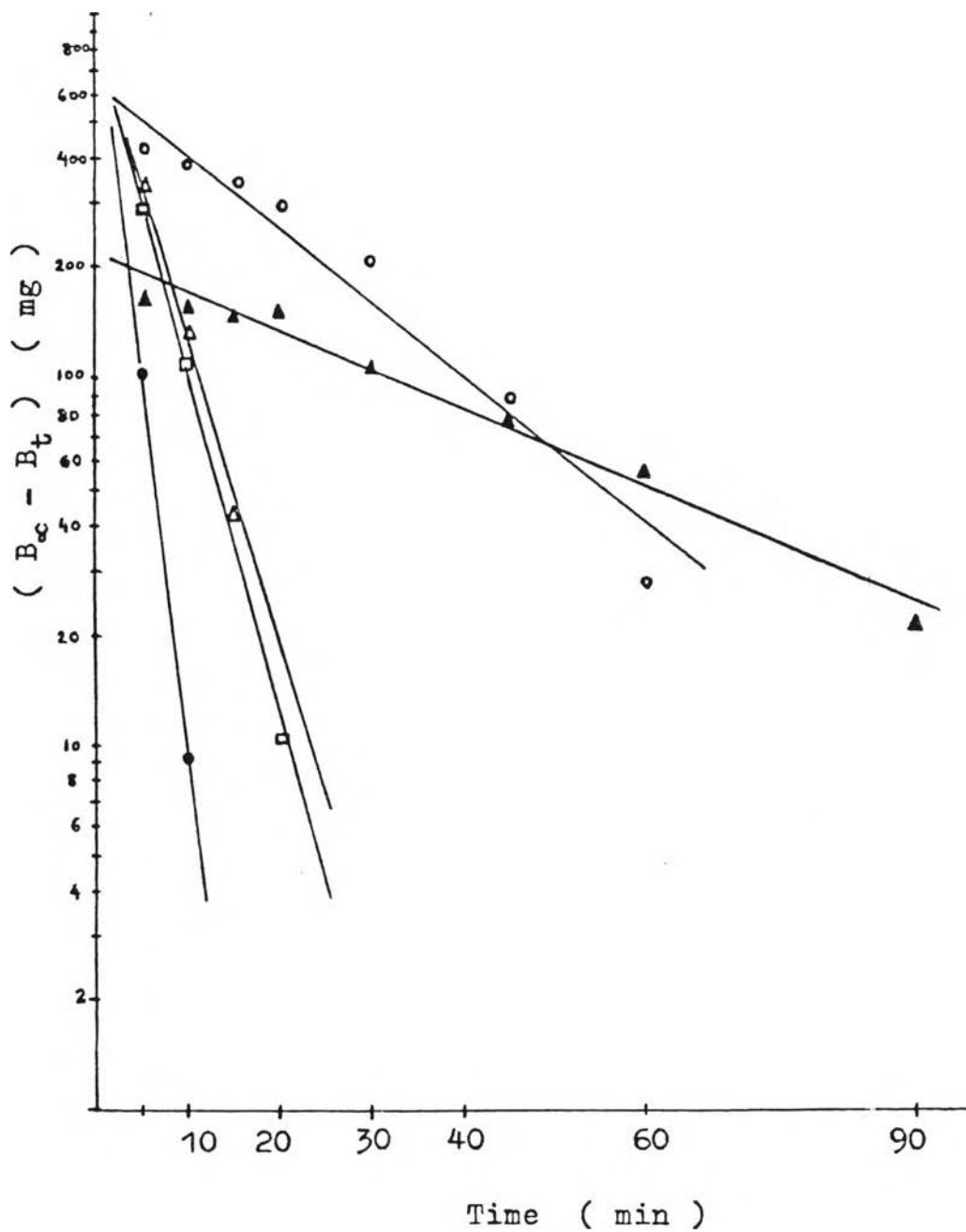| Brand	Dissolution rate constant (k) ($min.^{-1}$)						
	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	MEAN + S.D.
A	0.7640	0.1071	0.4796	0.4220	0.3667	0.1626	0.5443 ± 0.32
B	0.3778	0.3097	0.2356	0.3160	0.2594	0.2163	0.2858 ± 0.06
C	0.1409	0.3520	0.2470	0.2938	0.1906	0.1643	0.2314 ± 0.08
D	0.0607	0.05 0	0.0415	0.0386	0.0568	0.0497	0.0502 ± 0.01
E	0.0241	0.0252	0.0238	0.0238	0.0236	0.0242	0.0241 ± 0.00

Figure 3 The first order plot between amount of
undissolved cimetidine versus time for
five brands of cimetidine tablets.

Key : Brand A (●),   Brand B (□),
        Brand C (△),   Brand D (o),
        Brand E (▲).

Table 5   Analysis of Variance for Dissolution Rate
            Constant (k) of Five Commercial Cimetidine
            Tablets

Source of variation	d.f.	S.S.	M.S.	F
Among groups	4	1.0596	0.2649	11.5677
Within groups	25	0.5736	0.0229	
Total	29	1.6332		

$$F^{*}_{0.05} (4, 25) = 2.7587$$

d.f. = degree of freedom

S.S. = Sum of square

M.S. = mean square

F   = variation ratio

*Obtained from the table

Table 6 Comparison of Dissolution Rate Constants of
Local Manufactured Brands with Original
Brand (Brand A) by Student's t-test

Brand	t (Calculated)	t (Table)	Statistical significance
B vs. A	-1.9262	$t_{(0.05,5)} = 2.5706$	NS
C vs. A	-2.2990	$t_{(0.05,6)} = 2.4470$	NS
D vs. A	-3.7432	$t_{(0.05,5)} = 2.5706$	S
E vs. A	-3.9439	$t_{(0.05,5)} = 2.5706$	S

NS = not significant

S = significant

In Vivo Studies

Analysis of Cimetidine in Plasma Samples

Plasma cimetidine concentrations were analyzed by high pressure liquid chromatography . Typical chromatograms of cimetidine and internal standard are shown in Figure 4. Retention times for cimetidine and internal standard were 6.38 and 4.72 minutes, respectively. The analytical procedure was specific and reproducible. Analytical recoveries of cimetidine and procainamide were about 60%. The sensitivity of detection for cimetidine in plasma was 25 ng/ml. The coefficient of variation of within-day assay of plasma cimetidine levels was 3% at 1 μg/ml (n=6).

Clinical Observations

No side effects and/or any indication of intoxications were associated with administration of either cimetidine tablets or injections.

Plasma Cimetidine Level

For parenteral study : Individual plasma cimetidine concentrations from 9 subjects at appropriate sampling time from 0 to 6 hours are shown in Table 7. Following rapid bolus administration, plasma concentrations of cimetidine declined rapidly in the first hour (Figure 5) and then more slowly . This indicated that the plasma concentration-time profile was characterized by multi-
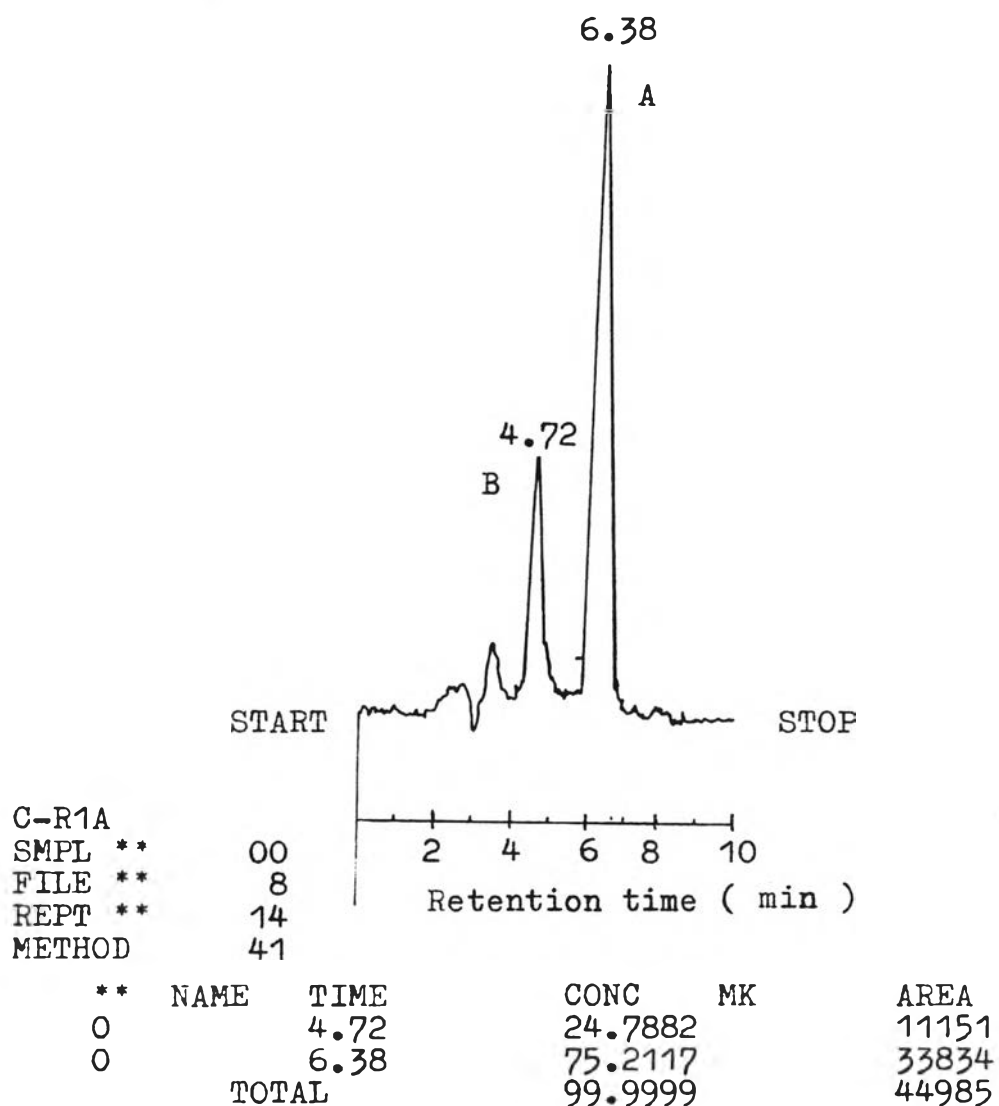
Figure 4   High pressure liquid chromatogram[a] of
cimetidine (A) and internal standard (B).

[a]Obtained from HPLC analysis of human plasma
containing 4 μg/ml of cimetidine and 20 μg/ml
of internal standard (procainamide).

compartmental kinetic (Figure 6).   Either a bi- or
triexponential function has been used to solve for the
mathematical model of the drug (26, 45).

For oral study   :   Plasma cimetidine concentration-
time profiles from 0 to 8 hours for brands A and B are
also presented in Table 7.   In this study, cimetidine
demonstrates unusually pharmacokinetic behavior.   As seen
a secondary peak in the plasma concentration profile after
oral dosing on a fasting stomach was produced which was
not observed after intravenous administration (Figures 5,
7, 8).   The first peak appeared at about 1 hour followed
by the second one at about 2 or 3 hours (Figures 7, 8)
after dosing.   Previous reports indicated that the
secondary peak will not present when cimetidine is taken
orally with food (26, 29-31, 46).   The reasons for this
aberrant phenomenon have been discussed by numerous
investigators (26, 29-31).

Veng Pedersen and Miller (29) suggested that the
secondary peak observed in the plasma level data can be
described best in terms of discontinuous reabsorption.
They developed a pharmacokinetic model to explain the
phenomenon which produced a resonably good fit to the
plasma concentration-time curve and proposed (based on
the model) the following interpretation :

1.   The secondary peak appears to be due to a
rapid release of cimetidine from a drug depot.   The depot
is located in a tissue or organ that is well perfused by

the drug in the first pass transfer. The bile and the hepatic parenchyma tissues are the most likely primary storage areas.

2. The time for the release appears to coincide with the intake of food in most cases. The 2 hours interval between oral drug intake and breakfast agrees well with the start of the secondary peak.

3. Drug transfer into the depot occurs mainly in the first pass process.

4. This transfer is significantly inhibited, possibly by the way of competitive active membrane transport, when the drug is taken with food. The excretion of bile in response to food also may play a role if the smaller amount of bile in the hepatic system reduces uptake rate or capacity of the system.

5. The transfer rate of drug into the depot from the systemic circulation is slow compared to the first pass transfer. This effect possibly is due to a pronounced drug concentration differences at the depot site for the two administration routes. The drug concentration is large in the first pass perfusion of the depot organ before the drug reach the general systemic circulation. However, when the drug is introduced parenterally in the systemic circulation, a substantial dilution takes place before it reaches the depot organ. The higher metabolic actively at the first pass route also may contribute to a larger uptake of drug by the depot.

Table 7   Individual Plasma Cimetidine Concentrations from 9 Subjects Following Intravenous and Oral Administration of Cimetidine.

| PRODUCTS	Time (hr)	1	2	3	4	5	6	7	8	9	MEAN	SE
							Subject No.					
200 mg injection	0.00	8.24	8.46	8.60	10.07	9.20	8.10	8.28	6.56	7.40	8.32	0.33
	0.25	3.70	4.04	4.96	4.49	4.76	5.73	4.97	3.85	4.34	4.53	0.21
	0.50	2.66	2.73	3.35	2.50	2.70	4.77	3.20	2.78	3.09	3.08	0.23
	0.75	2.05	2.12	2.49	1.96	2.31	3.25	2.33	2.13	2.21	2.32	0.13
	1.00	1.62	1.90	2.35	1.49	1.92	3.19	1.97	1.79	2.00	2.01	0.17
	1.50	1.31	1.74	1.79	1.17	1.58	2.24	1.15	1.41	1.20	1.53	0.13
	2.00	1.29	1.31	1.25	0.99	1.43	1.60	1.15	0.98	0.95	1.21	0.08
	3.00	0.85	1.01	0.84	0.54	0.98	0.68	0.70	0.80	0.52	0.77	0.06
	4.00	0.51	0.70	0.53	0.50	0.71	0.45	0.38	0.44	0.32	0.50	0.04
	6.00	0.21	0.35	0.24	0.13	0.36	0.19	0.14	0.33	0.08	0.22	0.03
400 mg tablet (Brand A)	0.50	1.23	0.33	0.25	1.29	3.87	1.61	5.52	1.92	2.56	2.06	0.57
	1.00	2.60	1.68	0.36	1.43	5.23	3.83	3.36	3.57	2.11	2.69	0.49
	1.50	2.43	3.27	1.89	1.46	3.69	1.89	3.44	2.45	2.56	2.56	0.26
	2.00	2.57	2.78	2.98	1.57	3.43	1.77	1.86	2.59	2.46	2.45	0.20
	3.00	2.63	2.88	2.74	1.69	2.49	2.87	1.49	1.91	2.26	2.33	0.17
	4.00	1.65	2.40	2.46	1.19	1.20	1.66	0.74	1.16	1.49	1.55	0.19
	6.00	0.46	1.17	0.61	0.46	0.74	0.73	0.33	0.54	0.64	0.63	0.08
	8.00	0.25	0.73	0.24	0.24	0.31	0.41	0.14	0.23	0.22	0.31	0.06
400 mg tablet (Brand B)	0.50	2.65	0.88	0.23	0.60	3.02	Trace[*]	0.38	0.11	1.32	1.02	0.37
	1.00	3.32	2.82	1.14	1.85	2.26	1.03	1.06	0.43	1.39	1.70	0.31
	1.50	2.34	2.59	2.82	1.88	3.70	2.95	1.31	0.65	1.67	2.21	0.31
	2.00	1.99	3.29	2.16	1.64	2.38	2.04	2.58	2.13	1.69	2.21	0.17
	3.00	2.49	2.24	2.41	2.19	2.62	2.09	3.17	3.57	1.82	2.51	0.18
	4.00	1.99	1.59	0.97	1.46	1.34	1.25	1.11	1.38	1.20	1.37	0.10
	6.00	0.88	0.96	0.34	0.82	0.58	0.70	0.59	0.58	0.98	0.71	0.07
	8.00	0.30	0.59	0.11	0.38	0.25	0.31	0.33	0.24	0.16	0.30	0.05

* < 0.025 µg / ml
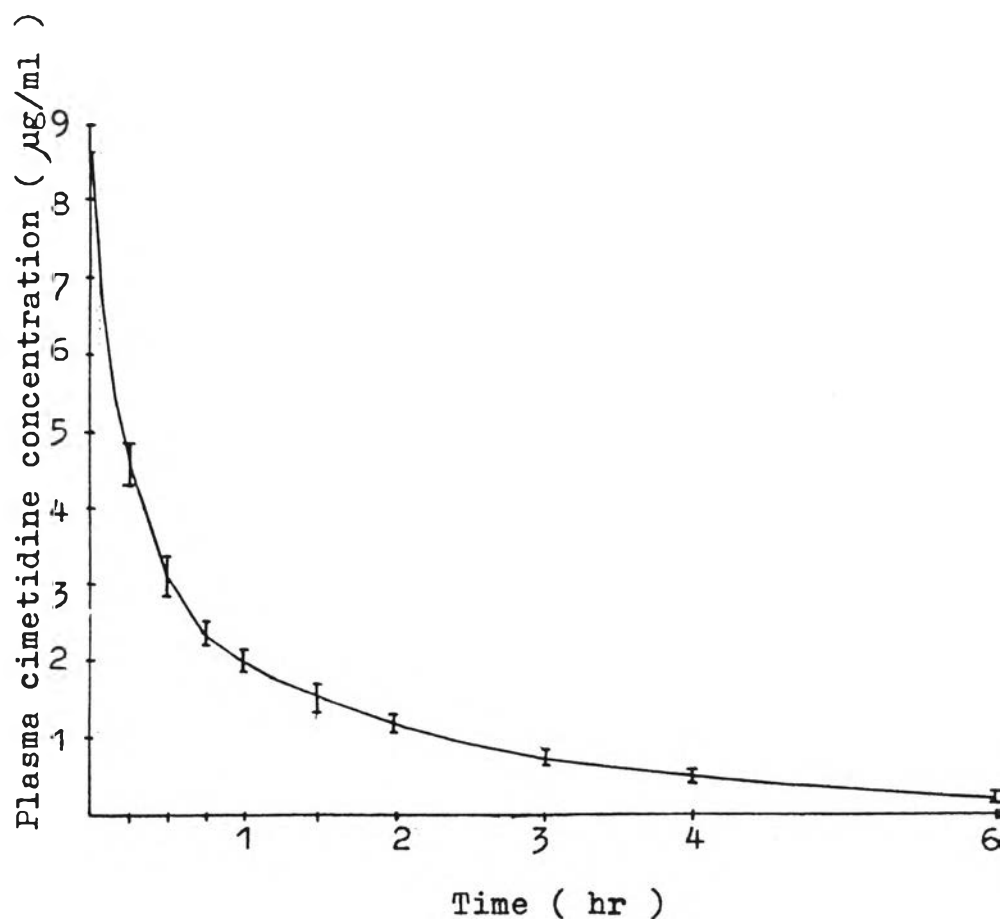
Figure 5 Plasma cimetidine concentrations (Mean$\pm$SE)
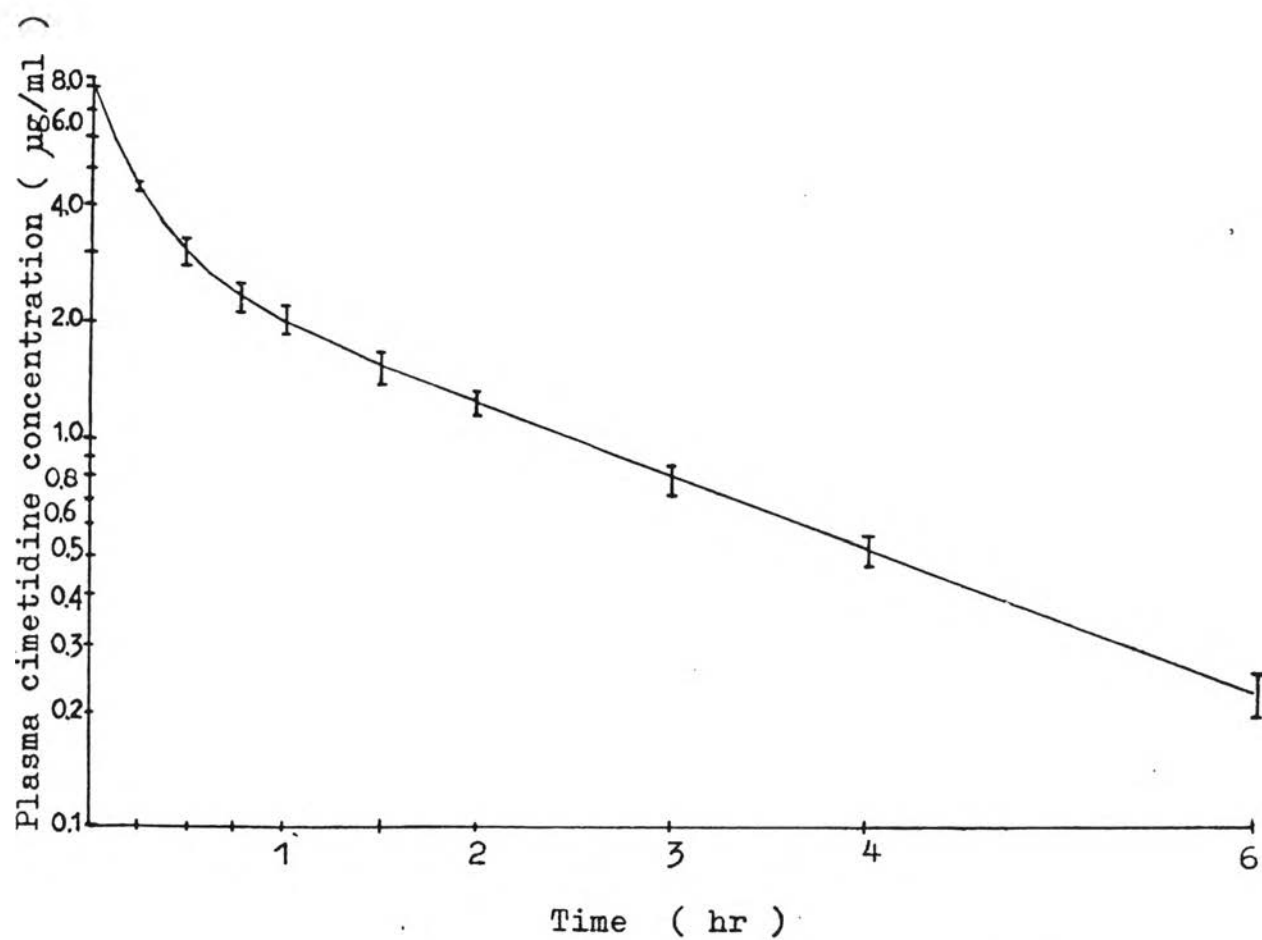from 9 subjects following intravenous
administration of 200 mg cimetidine.

Figure 6   Plasma cimetidine concentrations (Mean ± SE)

from 9 subjects following intravenous administration

of 200 mg cimetidine on semi-logalithmic scale.

6. Cimetidine possibly is stored in the depot both in the parent form and as conjugates or complexes. The large capacity of the hepatic system for storage and biliary excretion of conjugates may explain the magnitude of the secondary peak.

The secondary peak effect has also been observed by Grahnen et al. These authors suggested that the major metabolite of cimetidine, the sulphoxide, could be reduced back to the parent drug by human faecal bacteria with subsequent reabsorption (26). Support for the existence of a discontinuous absorption phenomenon for cimetidine in the rat has been reported by Griffiths et al. They found that cimetidine was well absorbed from the duodenum and ileum, less well from the jejunum and poorly from the colon (26).

In this study, four major characteristics of the blood level sequences of cimetidine were analyzed. They were : (1) the area under the blood level curve from zero to infinity, as a measure of drug availability ; (2) the first order absorption rate constant ; (3) the mean residence time ; (4) the time for which blood level remained above 0.5 μg/ml (this time was estimated by interpolation in the sequence of blood levels v.s. time). These values are presented in Table 9.
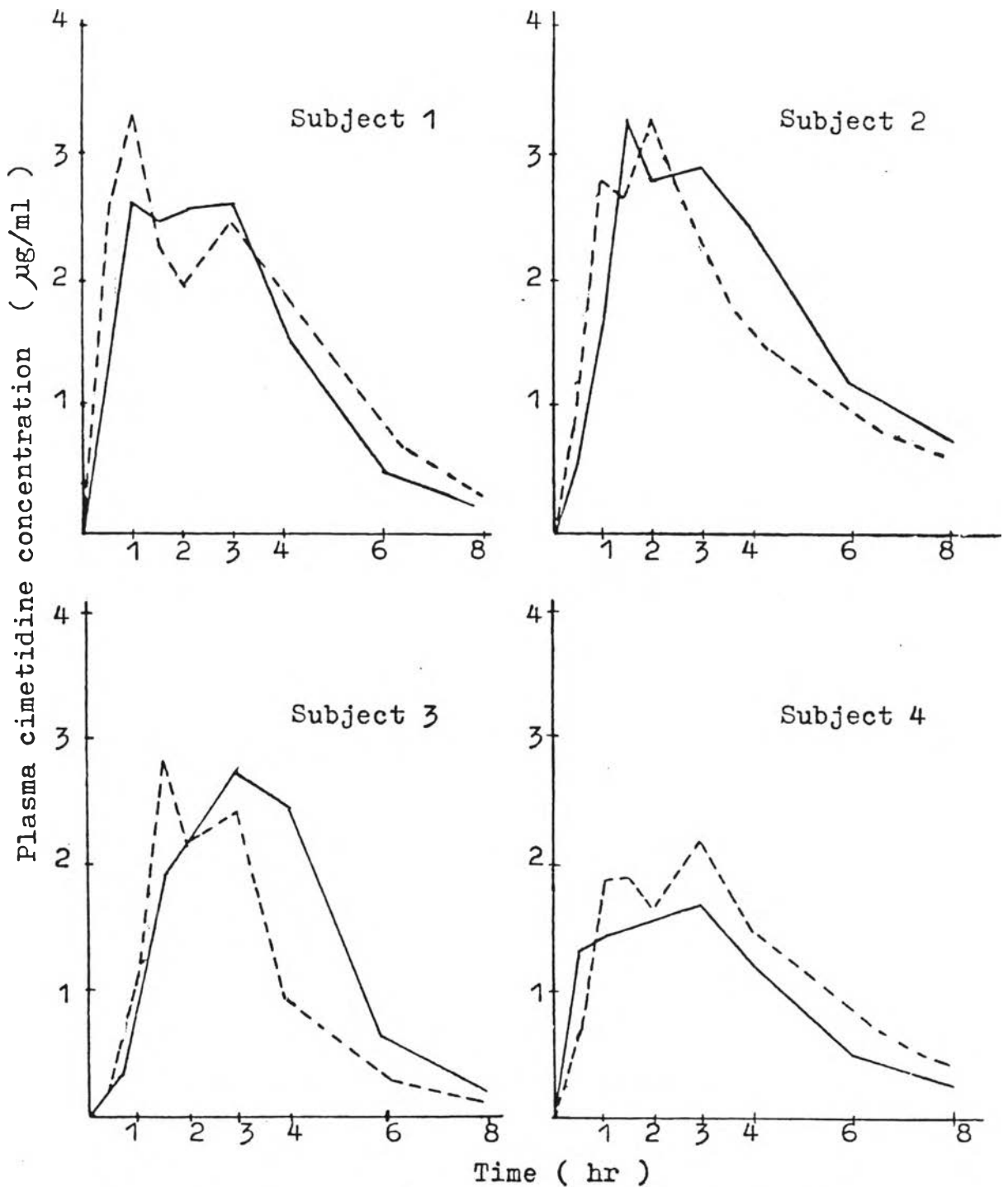
Figure 7   Plasma cimetidine concentration-time
            profiles of subjects 1-4 following oral
            administration of two different brands
            of cimetidine (Brands A and B)
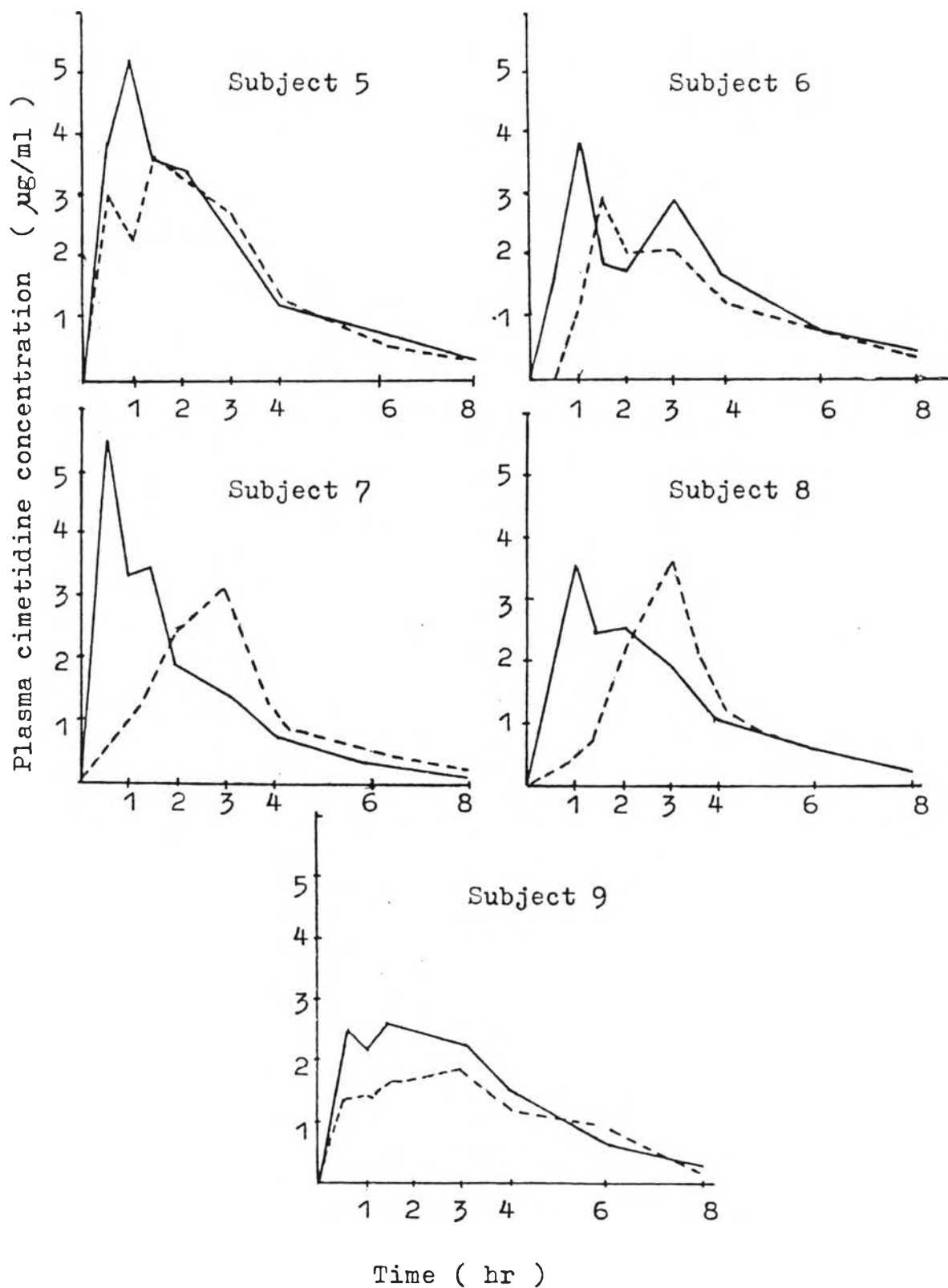   Key : Brand A (———),   Brand B (----)

Figure 8   Plasma cimetidine concentration-time profile of
subjects 5-9 following oral administration of
two different brands of cimetidine (Brands A and B)
Key : Brand A (————),   Brand B (— — — —)

Area Under Plasma Level - Time Curve

The area under the curve, AUC, and the area under
the first moment curve, AUMC, from zero to infinity after
intravenous and oral administrations are reported in
Table 8.

The mean $[AUC]_0^\infty$ after intravenous administration
was 8.19 μg-hr/ml while those after oral administrations
ranged from 11.24 μg-hr/ml to 12.51 μg-hr/ml.
Statistical analysis of difference among $[AUC]_0^\infty$ values
indicated that there were no significant difference
observed between Brands A and B (p $>$ 0.05).

Bioavailability of Cimetidine

The bioavailability of drug from tablet dosage
forms not only depends on the rate but also the extent of
drug absorption into the general circulation (41,44).
These factors can be evaluated by determining the pharmaco-
kinetic parameters derived from blood level-time profiles
for an unchanged drug. The most commonly used method for
estimating availability is the comparison of the total
area under the drug concentration in plasma versus time
curve, AUC, after oral administrations of the test
formulation and the reference product (41).

Estimation of absolute bioavailability after oral
administration always requires comparison with data obtained
after intravenous administration. Various oral standards

have been used to determine relative bioavailability.
These include certain commercial formulations that are
generally accepted as standards. Although relative
bioavailability studies are useful for characterizing the
formulation, one must determine absolute bioavailability
to characterize the drug.

Based on the area under the curve method, the mean
absolute bioavailabilities were 76.13 $\pm$ 3.54 % (Mean $\pm$ SE)
for Brand A, and 71.15 $\pm$ 4.62 % (Mean $\pm$ SE) for Brand B.
This is in accordance with a value around 70 % as reported
previously (1,22-23,47). This incomplete bioavailability
appears to be due to a first pass effect (29) and/or
stability of cimetidine in gastrointestinal tract (19).
The mean relative bioavailability of cimetidine Brand B
with respect to Brand A was 94.23 $\pm$ 6.54 % (Mean $\pm$ SE).

The quantities of cimetidine absorbed, $[AUC]_0^\infty$,
for Brands A and B were no statistically significant
difference (p $>$ 0.05) between each other (Table 11).
This parameter was in agreement with the values of
2.98 $\pm$ 0.98 and 2.71 $\pm$ 0.56 μg-hr/ml/100 mg as reported
by Somogyi et al. and Gugler et al. (26), respectively.

Table 8 Individual Pharmacokinetic Parameters of

Cimetidine from 9 Subjects Following 200 mg

Intravenous and 400 mg Oral Administrations.

Injection

Subject No	[AUC]$_0^\infty$ (ug hr / ml)	[AUMC]$_0^\infty$ (ug·hr^2/ ml)	MRT (hr)	$t_{1/2}$ (hr)
1	7.6490	15.1261	1.9775	1.37
2	9.1725	22.2134	2.4217	1.68
3	8.8235	16.3153	1.8490	1.28
4	7.0456	11.1949	1.5889	1.10
5	9.5022	22.3741	2.3546	1.63
6	9.8260	15.1300	1.5398	1.07
7	7.4901	11.5820	1.5463	1.07
8	7.7025	17.8510	2.3176	1.61
9	6.5244	8.8736	1.3601	0.94
X	8.1929	15.6289	1.8839	1.31
SE	0.3885	1.5654	0.1345	0.09

Brand A

Subject No	[AUC]$_0^\infty$ (ug·hr / ml)	[AUMC]$_0^\infty$ (ug·hr^2/ ml)	MRT (hr)	MAT (hr)	Ka (hr^{-1})
1	11.8427	37.7178	3.1849	1.2074	0.8282
2	16.7083	78.0428	4.6709	2.2492	0.4446
3	11.7888	42.3737	3.5944	1.7454	0.5729
4	8.5025	30.4375	3.5798	1.9909	0.5023
5	15.7856	45.1872	2.8626	0.5080	1.9685
6	13.3939	49.7183	3.7120	2.1722	0.4604
7	11.2593	25.5164	2.2663	0.7200	1.3889
8	11.4201	34.6824	3.0370	0.7194	1.3900
9	11.9133	37.0866	3.1130	1.7529	0.5705
X	12.5127	42.3070	3.3357	1.4517	0.9029
SE	0.8272	5.0957	0.2230	0.2250	0.1826

Brand B

Subject No	[AUC]$_0^\infty$ (ug·hr / ml)	[AUMC]$_0^\infty$ (ug·hr^2/ ml)	MRT (hr)	MAT (hr)	Ka (hr^{-1})
1	13.8208	45.8970	3.3209	1.3434	0.7443
2	14.8546	65.3901	4.4020	1.9803	0.5050
3	8.5737	25.9993	3.0324	1.1834	0.8450
4	10.9126	45.3834	4.1588	2.5699	0.3891
5	12.9102	39.2691	3.0417	0.6871	1.4554
6	10.0328	39.4046	3.9276	2.3878	0.4188
7	10.7195	36.9338	3.4455	1.8992	0.5265
8	9.7780	37.3983	3.8247	1.5071	0.6635
9	9.5175	33.7125	3.5423	2.1822	0.4583
X	11.2355	41.0431	3.6329	1.7489	0.6673
SE	0.7126	3.6348	0.1600	0.2047	0.1110

Table 9 Pharmacokinetic Parameters (Mean $\pm$ SE) of Cimetidine from 9 Subjects Following

200 mg Intravenous and 400 mg Oral Administrations.

Parameter	Injection 200 mg i.v.	Brand A 400 mg oral	Brand B 400 mg oral
Area under the plasma concentration-time curve from the time zero to infinity, $[AUC]_0^\infty$ (μg·hr/ml)	8.19 $\pm$ 0.38	12.51 $\pm$ 0.83	11.23 $\pm$ 0.71
First order absorption rate constant, K_a (hr^{-1})	—	0.90 $\pm$ 0.18	0.67 $\pm$ 0.11
Mean residence time, MRT (hr)	1.88 $\pm$ 0.13	3.34 $\pm$ 0.22	3.63 $\pm$ 0.16
Time for which blood level remained above 0.5 μg/ml (hr)	4.25 $\pm$ 0.20	6.35 $\pm$ 0.37	6.33 $\pm$ 0.30

Absorption of Cimetidine Tablet

The absorption data, obtained from individual plasma data of 9 subjects following oral administration of 400 mg cimetidine tablets for Brands A and B, are summarized in Table 8. The Student's t-test ($p < 0.05$) were performed for significant differences between related parameters.

The first order absorption rate constants (K_a), for Brands A and B were 0.90 ± 0.18 and 0.67 ± 0.11 hr^{-1}, respectively. When comparing these mean absorption rate constants between Brands A and B, no statistically significant difference were observed ($p > 0.05$).

Mean Residence Time

The mean residence time, a function of how a drug is administered, represents the time for 63.2 % of the administered dose to be eliminated irrespective of the distribution characteristics of drug (41). For intravenous data, the average mean residence time was 1.88 ± 0.13 hours and the mean effective half-life was 1.31 ± 0.09 hours (Table 8). These values were not much different from other studies. As examples, Lebert et al. (48) studied 8 normal subjects after a single intravenous dose of cimetidine. Subjects ranged in age from 21 to 35 years; had mean half-life 1.5 ± 0.3 hours. Bauer et al. (49) investigated cimetidine kinetics in 6 normal subjects after a single intravenous dose. Subjects ranged in age

from 28 ± 4 years; had mean half-life 1.9 hours and mean
residence time, MRT , 2.3 hours. However, the mean half-
life and MRT in this study slightly differed from those
reported by Bauer et al. The reason for this is that
half-life and renal clearance of the drug are depened on
population and age. The changes in pharmacokinetic
parameters with age were thought to be due to decreased
renal function in the older subjects (45,49).

For oral study of 400 mg cimetidine tablet, Bra ds
A and B yielded almost the same MRT values (Table 8 and 9)
and there were no statistically significant difference
between each others (p > 0.05).

Time For Which Blood Level Remains Above 0.5 µg/ml

A blood concentration of 0.5 µg/ml cimetidine has
been shown to produce a 50 percent reduction of maximal
stimulated acid output. This level probably is of
relevance for therapeutic efficacy and can be regarded as
a goal in dosing for ulcer healing (1,9,26,28). The time
periods, during which the plasma concentration was sustained
above this level for each product are presented in Table 10.

In most subjects, levels in excess of 0.5 µg/ml
were maintained for at least 4 hours after 200 mg cimetidine
intravenous administration. In the case of oral study,
the time for which the blood level remained above 0.5 µg/ml
was identical for Brands A and B (p > 0.05) and was about
6 hours. Therefore 400 mg cimetidine tablet is not

Table 10 Time[1] for Which Blood Level Remains Above
0.5 µg per ml for Cimetidine Tablets and
Injection (hr).

Subject No.	Injection 200 mg i.v.	Brand A 400 mg oral	Brand B 400 mg oral
1	4.00	5.75	7.00
2	4.90	8.50	8.00
3	4.30	5.50	5.25
4	3.40	5.75	6.75
5	5.00	6.88	6.13
6	4.00	7.50	6.25
7	3.50	4.88	5.63
8	4.25	6.13	5.25
9	4.90	6.25	6.75
$\bar{X}$	4.25	6.35	6.33
± SE	0.20	0.37	0.30

[1] This time was estimated by interpolation in the
sequence of blood levels vs time.

necessary administered as frequently as antacid because of this somewhat long period in inhibiting acid output.

In Table 10, the results showed that seven of nine volunteers attained or exceeded the 0.5 μg/ml blood level of cimetidine within 30 minutes after oral dosing of Brand A but five of nine subjects for Brand B. This may be due to the difference in In Vivo dissolution time between these 2 brands. However, the mean plasma concentrations of both brands obtained from 9 subjects reached 0.5 μg/ml within 30 minutes. This time was comparable with those reported previously for cimetidine by other investigators. Bodemar et al. (50) reported that the time periods for which the plasma level remained above 0.5 μg/ml ranged from 1.4 to 5.0 hours after 200 mg intravenous administration and ranged from 2.2 to 7.2 hours after 400 mg cimetidine oral administration.

The similarities of the plasma level versus time curves and related pharmacokinetic parameters for Brands A and B indicates that these two brands are bioequivalent and may be used interchangeably. It can be assured that Brand B, the local manufactured brand of cimetidine tablets are essentially equivalent to an original formulation although it was the least retail price product.

Table 11 Comparison of Pharmacokinetic Parameters after
Oral Administration of Brand B with Brand A by
Student's t-test.

Parameters	t calculated Brand B vs Brand A	Statistical significance
Area under the concentration-time curve, $[AUC]_0^\infty$ (μg-hr/ml)	-1.1696	NS
Apparent first order absorption rate constant, K_a (hr^{-1})	-1.1025	NS
Mean residence time, MRT (hr)	1.0828	NS
Time for which blood level remains above 0.5 μg/ml, (hr)	-0.0420	NS

$t_{(0.05,16)} = \pm 2.1199$

NS = not significant