BIO/DSS

REVIEW

12.1

Enalapril Maleate (MK-421)
Vasotec^{R}
Tablets; 5, 10, 20, 40mg
NDA 18-998
1 0
Wang #4324x

Merck, Sharp & Dohme
West Point, Penn. 19486
Submission Dated:
April 15, 1985

MAY 22 1985

Review of NDA Amendment

This submission contains information requested from the firm by The Division of Biopharmaceutics. A desk copy was also received and reviewed, thus this submission is being returned. Refer to submission dated January 31, 1984 for further information.

/S/

Gene D. Mason, Pharm.D.
Pharmacokinetic Review Branch

RD Initialed by M.Y.Huang, Ph.D.
FT Initialed by C.T.Viswanathan, Ph.D. CTV 5/21/85

cc: NDA 18-998 orig., HFN-110 (2), HFN-226 (Mason), Chron, Division, Drug and Review Files.

GDM/kek/#4324x (05/20/85)

Enalapril Maleate (MK-421)
Vasotec^{R}
Tablets; 5, 10, 20, 40 mg
NDA 18-998
Reviewer: Gene D. Mason, Pharm. D.
Wang #2639x

Merck, Sharp & Dohme
West point, Penn. 19486
Submissions Dated:
January 31, 1984
February 6, 1985-
April 4, 1985
[redacted]

MAY 22 1985

Review of NDA*

I. BACKGROUND

The Division of Biopharmaceutics has no record of previous submissions from the sponsor regarding enalapril maleate (MK-421).

MK-421 is the maleate salt of enalapril. Enalapril, the monoethyl ester of enalaprilic acid, is a prodrug which is hydrolyzed to the active diacid moiety enalaprilic acid (MK-422). MK-422 is an angiotensin converting enzyme inhibitor indicated in the treatment of hypertension and congestive heart failure.

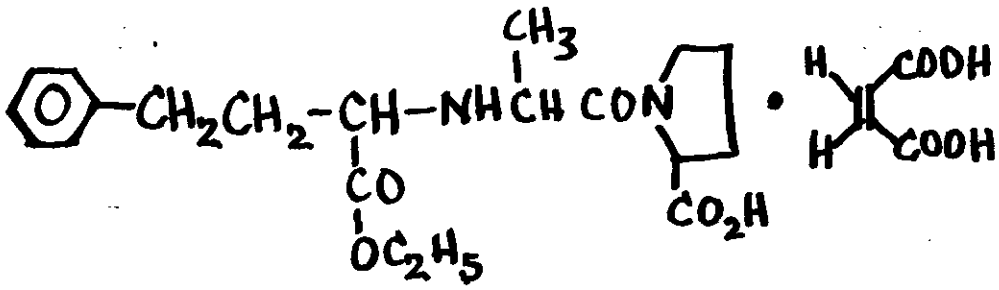
Glossary of Names

Enalapril Maleate (E.M.)	Nonproprietary name adopted by the USAN council; equivalent to the terms L-154,739 and MK-421.
Enalaprilic Acid (E.A.)	Refers to the active diacid of enalapril maleate; equivalent to the terms L-154,628, MK-422 and enalaprilat (the proposed nonproprietary name for this moiety).
Enalapril	The monoethyl-ester of enalaprilic acid.
Total Drug (T.D.)	Enalaprilic acid measured in biological fluids after hydrolysis; represents that which was present in the sample as enalaprilic acid itself plus that which was present as enalapril.

Equivalence: 1.308 mg E.M.= 1.0 mg enalapril free base = 0.926 mg E.A.

*Tables and graphs pertaining to the review of this submission are contained in copies sent to HFN-110 and stored in Chron and Drug Files.

II. CHEMISTRY: The structure and chemical name of enalapril maleate is below.



(S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1)

Empirical Formula - $C_{20}H_{28}N_2O_5$ $C_4H_4O_4$ pKa - 3.0 and 5.4

Molecular Weight 492.53

Solubility - 25 mg/ml H_2O at ambient temperature
Freely soluble in methanol and dimethylformamide; soluble in ethanol; slightly soluble in semi-polar organic solvents; insoluble in non-polar organic solvents; sparingly soluble in water.

The pH solubility profile(Figure 1a) indicates the solubility of MK-421 increases with pH.

Formulation - Tables 2a, 2b and 2c provide formulations for tablets and IV preparations used in clinical studies. Table 2d contains formulations for the proposed dosage forms. Below is an outline of studies by formulation and preparation.

A. Capsule Preparation Studies

Reference	Study/Investigator	Dosage Form/Strength	Formulation #
3	#512	Capsule	
		MK-421 10 mg	MR-1548
		MK-422 10 mg	MR-1549
		MK-521 10 mg	MR-1550
5	#503	Capsule	
		MK-421 10 mg	80-55-04
		MK-521 10 mg	--
6	#518	Capsule	
		MK-421 10 mg	80-55-11
8	#555	Capsule	
		MK-421 2.5 mg	80-55-24
		10 mg	80-55-26
		40 mg	80-55-28
		I.V.	
		MK-422 5 mg	--
12	#523	Capsule	
		MK-421 10 mg	80-55-20
		I.V.	
		MK-422 5 mg	0421 HSS 001 B03
15	#17	Capsule	
		MK-421 10 mg	0421-DFC-001-B03
16	#570	Capsule	
		MK-421 10 mg	80-55-20
17	#634	Capsule	
		MK-421 10 mg	80-55-26
18	#618	Capsule	
		MK-421 10 mg	80-55-37

B. Tablet Preparation Studies

Reference	Study/Investigator	Dosage Form/Strength	Formulation #
9	#110	Tablet	
		MK-421 10 mg	0421-OCT-026-B01
10	#168	Tablet	
		MK-421 5 mg	0421-OCT-025-C004
		MK-421 10 mg	0421-OCT-026-B010
		MK-421 20 mg	0421-OCT-007-D010
		MK-421 40 mg	0421-OCT-007-E006
		I.V.	
		E.Maleate 5 mg	0421-HSS-005-A06
		E.Acid 5 mg	0422-HSS-001-A05
13	#27	Tablet	
		MK-421 10 mg	0421-OCT-009-B02
		I.V.	
		MK-422 5 mg	0421-HSS-001-B03
14	#23	Tablet	
		MK-421 40 mg	0421-OCT-006-E01

*This study utilized the proposed marketed preparation(that used in pivotal clinical efficacy and safety studies).

C. Tablet and Capsule Preparation Studies

Reference	Study/Investigator	Dosage Form/Strength	Formulation #
11	#53	Tablet	
		MK-421 10 mg	0421-OCT-026-B01
		Capsule	
		MK-421 10 mg	0421-DFC-001-B07

D. Intravenous Preparation Studies

Reference	Study/Investigator	Dosage Form/Strength	Formulation #
4	#6	IV	
		MK-422 2.5, 5, 10	

D. 'Similar' Tablet preparations (see tables 2a, 2b, 2b-2 in this review)

I*	II	III
(#53)	(#110)	#23)
(#27)		
(#168)		

* These formulations are most similar to the proposed tablet formulation (see table 2d in this review)

E. 'Similar' Capsule preparations (see tables 2b and 2b-1 in this review)

I	II	III	IV
(#523) (#555) (#570)	(#53)	(#503)	(#518)

In a telephone conversation with a representative of the firm (Dr. David Blois) on 1/28/85 it was learned that pivotal clinical studies were performed using the tablet formulation. Drs. Alice Till and K.C. Kwan informed the Agency in a telephone conversation on 04/05/85 that the tablet preparation in study #168 is the proposed marketed formulation and is also that used in pivotal clinical efficacy and safety studies. The firm submitted a statement showing the relationship between formulations used in BA studies and those used in pivotal clinical studies of efficacy. This information is given in Tables 2d-1, 2d-2, and 2d-3.

III. DISSOLUTION

Method - USP apparatus II (paddle), 50 rpm, 900 ml water, 37°C; min. sampling (capsules and early tablet formulations used 750 ml of water instead of 900 ml).
Assay

Table 1 contains a summary of drug product dissolution data. Individual dissolution profiles were not provided.

Proposed Dissolution Method:
USP apparatus II (paddle) at 50 rpm, 900 ml water, 37°C
specification - at least % dissolution in minutes.

IV. ADMINISTRATION/DOSING

Tablets: 5, 10, 20, 40 mg (see Tables 2d and 6).
Usual Dose Range: 10-40 mg/day; QD or BID dosing.

V. RESULTS:

Pharmacokinetics:

#555 - (MK-422)
#523 - (MK-422)
#168 - (MK-421 and 422)
27 - (MK-422)

MK-422 has multicompartmental disposition. A terminal half-life of approximately 40 hours has been described. The firm proposed that the terminal phase represents saturable binding to angiotensin converting enzyme (ACE) and showed that the terminal phase observed in dogs can be eliminated by coadministering enalapril with captopril. Table 7 contains individual MK-422 serum concentrations observed after IV administration of MK-422 alone and with captopril in dogs. The same data is displayed graphically in figure 4. Similarly, table 8 contains individual data for coadministration of enalapril and captopril in dogs. Figure 2 graphically shows loss of the terminal phase when enalapril and captopril are coadministered. The mechanism is reported to be competitive binding to angiotensin converting enzyme. No data obtained in humans were submitted. It was explained that the dispositon of MK-422 is determined by two separate pharmacokinetic processes, one linear and the other non-linear (saturable binding to ACE).

Parameters - (MK-422)
Cl (total) - No value reported
Cl (renal) - 148 ml/min in normal subjects on average (study #6)
Volume of distribution - No value reported
half-life - The firm states that the terminal T1/2 is roughly 40 hours; the disposition half-life for other compartments has not been characterized;The "accumulation" half-life with single daily dosing is approximately 11 hours.

Bioavailability Studies

For the purpose of this review the term "availability" refers to the amount or fraction of the dose that is absorbed and converted to enalaprilic acid systemically.

(study #512) showed that enalapril maleate (E.M.) is better absorbed than enalaprilic acid. Less than 5% of an oral dose of enalaprilic acid could be accounted for in urinary collections. Absorption of enalapril after administration of E.M. ranges from 60-70 percent. Approximately 60% of enalapril absorbed is hydrolyzed to enalaprilic acid. Availability of active MK-422 is 41% on average in healthy patients with normal renal function. After an oral dose MK-421 serum concentrations peak in approximately 1 hour, whereas MK-422 serum concentrations peak in approximately 4 hours. Therefore, hydrolysis of MK-421 to MK-422 appears to be the rate limiting step for avilability of MK-422. The fate of unabsorbed drug was discussed with representatives of the firm(Drs. A.Till & C.Kwan) in a telephone conversation on 04/04/85. It was learned that in an independent investigation by the firm, 6% and 27% of the dose administered was recovered in the feces as MK-421 and MK-422, respectively. This suggests that parent drug is hydrolyzed in the gut to the nonabsorbable active species - MK-422.

study		absorption (fraction)	hydrolysis	availability
#168 -	(tab)	0.59 - 0.73	0.60 - 0.62	0.36 - 0.44
# 27 -	(tab)	0.59	0.68	0.40
#555 -	(tab)	0.52	0.61	0.32
#503 -	(cap)	0.61	0.70	0.43
#523 -	(cap)	0.78	0.72	0.56
# 53 -	(cap)	0.61	0.68	0.42
	(tab)	0.63	0.63	0.40

Dose Proportionality Studies:

#168 - (IV)
#555 - (capsule)

The observed increase in the area under the serum concentration vs. time curve with increasing dose is less than proportional (studies #6 and #555). This is postulated to be secondary to saturable binding of E.A. to ACE and is reflected in the prolonged terminal phase. To eliminate this phenomenon the AUC extrapolated from time 0 to infinity using the terminal slope was subtracted from the total AUC (This procedure was performed in studies #6 and #168). This resulted in a proportional increase in AUC with increasing dose in study #6. Figure 168-1 in this review shows the relationship of AUC (0-infinity) to availability of MK-422.

In summary, the change in AUC is not proportional to the change in dose. The cumulative % of the dose excreted in the urine is constant across the dose range 10 to 40 mg. Based on urinary recovery of drug, the "availability" of MK-422 is not significantly different across the dose range 10 to 40 mg.

Bioequivalency Studies:

#53 - (tablet vs. capsule)

There was no significant difference (P greater than 0.05) between tablets and capsules in Total Urinary Recovery of MK-422 and Total Drug. Similarly, no significant difference was observd for C_{max}, T_{max}, and AUC (0-72 hrs.). However, for the parameter Total Drug, the power to detect a 20% difference between treatments (alpha = 0.05) is 0.65 and to detect a 25% difference is 0.86. For the parameter MK-422(urinary recovery), the power to detect a 20% difference is 0.71 and to detect a 25% defference is 0.90. 75/75 ratio comparison of urinary recovery of Total Drug, AUC(0-72 hrs.) and urinary recovery of MK-422 resulted in 72.7% (8/11) within 75-125% for both parameters. As for conversion of MK-421 to MK-422, urinary recovery ratios of MK-422 to Total Drug following oral administration of Mk-422 tablets and capsules resulted in 91%(10/11) within 75-125%.

Chronic Dosing Studies:

#518 - (capsule)

Based on repeated single daily doses of enalapril capsules (study #518), an accumulation ratio of 1.3 was calculated (C_{min} at SS/C_{min} 1). Urinary recovery of MK-422 on day 8 was 39% whereas total recovery as a percent of all doses administered was 45% (statistical significance not stated). These values are consistent with those for availability observed in other studies (#168, 503, 523, 27).

Metabolism Studies:

#512 - (capsule)

Figure 1 shows the metabolic pathway for enalapril. Enalapril undergoes little metabolism other than hydrolysis of MK-421 to MK-422. Approximately 14% of an IV dose of enalapril maleate was not accounted for by total urinary recovery and 10% of an IV dose of enalprilic acid was not accounted for by total urinary recovery studies (#168). Unidentified metabolites were also found using thin-layer chromatography (#6). These observations suggest limited metabolism of the drug.

The role, if any, of biliary excretion has not been fully investigated. Urinary recovery of MK-422 after IV administration of MK-422 was 92, 96, 93% recovery with 2.5, 5, and 10 mg doses respectively (#6 Ferguson). This is consistent with little or no biiary excretion of MK-422 after administration of MK-422. Although there is no direct evidence in humans of biliary excretion of drug after administration of MK-421, evidence obtained by (#168) showed that a mean 86% of an intravenous dose of MK-421 was accounted for in total urinary collection. In addition, fecal recovery of MK-422 may be due to incomplete absorption of MK-421, biliary excretion of MK-421 or both. Data obtained in a perfused rat liver preparation showed that approximately 23% of a dose of MK-421 appeared in the bile whereas 5% of the MK-422 dose appeared in the bile. These findings suggest that MK-421 penetrates hepatocytes which facilitates elimination in bile. In contrast, the hepatic extraction of MK-422 was low in this experimental model (K Pang, et.al., Disposition of Enalapril and its Diacid Metabolite, Enalaprilat, in a Perfused Rat Liver Preparation - Presence of a Diffusional Barrier for Enalaprilat into Hepatocytes, Drug Metabolism and Disposition, 12(3): 309, 1984).

Effect of Disease States on Drug Dispostion:

#110 - (tablet): renal impairment

Renal impairment results in substantial accumulation of the drug. There is also an increase in the extent of hydrolysis of MK-421 to MK-422 and thus an increase in "availability" of active drug (MK-422). Dose adjustment is necessary in patients with renal impairment.

Interaction Studies:

#23 - (tablet): effect of food
#618 - (capsule): furosemide
#17 - (capsule): hydrochlorothiazide (HCTZ)
#570 - (capsule): propranolol
#634 - (capsule): digoxin

Food - Coadministration of E.M. with food did not affect the availability of MK-422.

Furosemide - Coadministration of E.M. with furosemide did not influence the availability of MK-422.

Hydrochlorothiazide - Concomitant administration of E.M. and HCTZ under steady state conditions resulted in a decrease in extent of absorption of HCTZ. The extent of absorption of HCTZ following a single dose is not significantly altered when coadministered with E.M. at steady state. An increase (not significant) in C_{max} (56.1 vs 68.2 ng/ml) and a decrease in T_{max} (4.4 vs 3.9 hrs.) values for MK-422 were noted after addition of a single dose of Mk-422 to HCTZ under steady state conditions.

Propranolol - When single doses of propranolol and E.M. were coadministered the extent of absorption of propranolol increased approximately 10%. Based on urinary recovery of total drug, the extent of absorption of E.M. decrease approximately 30% when coadministered with propranolol (53 vs. 36%). The extent of hydrolysis of MK-421 to MK-422 was similar for the two treatments (0.66 vs. 0.68). Thus, the availability of MK-422 is less when E.M. maleate is coadministered with propranolol.

Digoxin - There was no significant difference in availability of MK-422 when E.M., 10 mg PO, was coadministered with a single 0.25 mg oral dose of digoxin. The impact on the bioavailability of digoxin was not assessed.

Protein Binding Studies:

Protein binding characteristics of enalaprilat (MK-422) was investigated by equilibrium dialysis (ED) and ultrafiltration (UF). Binding in human plasma exhibited biphasic Scatchard plots. High affinity binding predominated at total concentrations less than approximately 20 nM (8 ng/ml) whereas low affinity binding predominated above 30 nM (12 ng/ml). Data obtained by UF are presented in Table 10 and Figure 5. Data obtained by ED are presented in Table 11 and Figure 6.

It was reported that independent studies by the firm measured angiotensin converting enzyme concentrations in human plasma as approximately 5 nM. The firm concluded that high affinity binding corresponds to binding to plasma angiotensin converting enzyme because of the agreement with the capacity of the high affinity binding. In a telephone conversation with a representative of the firm (Dr. Alice Till) on 1/24/85 it was suggested that low affinity binding corresponds to binding to albumin. However, the identity of the low affinity binding protein was not given in this report.

A. Ultrafiltration

In the total concentration range [nM ( ]ng/ml*) binding decreased from approximately 78% to 60% as concentration increased. In the total concentration range [nM [ ]ng/ml) binding decreased from approximately [% as concentration increased.

High affinity binding	Low affinity binding
Kd = 2.2 nM	Kd = 1500 nM
Capacity = 10 nM	Capacity = 1500 nM

B. Equilibrium Dialysis

In the total concentration range [nM ( ]ng/ml*) binding decreased from approximately 70% to 45% as the concentration increased. In the total concentration range [nM [ ] ng/ml) binding decreased from approximately [% as concentration increased.

High affinity binding	Low affinity binding
Kd = 5.1 nM	Kd = 720 nM
Capacity = 15 nM	Capacity = 460 nM

In conclusion, plasma binding is concentration dependent. In the ultrafiltration experiment binding ranged from [% over the clinical concentration range and in the equilibrium dialysis experiment ranged from percent.
(*concentrations are approximations)

VI. ASSAY METHODOLOGY

VII. COMMENTS:

In general,

1. The pharmacokinetic disposition of the drug has been characterized. However, several less critical parameters were not described. Although the terminal half-life has been described, the preceeding half-lives have not, including the distribution half-life observed after IV dosing. Although MK-422 is primarily renally eliminated and renal clearance is given, total clearance was not given. No volumes of distribution (Vd) are given (volume of central compartment, VD (steady state), Vd area).

2. Mean dissolution and ranges are given in Table 1 of this review. Note that dissolution is consistently rapid and has a narrow range.

3. HFN-110 should note the following:

   Water was the only dissolution media used in dissolution studies. In a telephone conversation with the firm it was learned that dissolution in other media was not investigated. It is normally recommended that dissolution profiles be provided in simulated gastric fluid (without enzymes), simulated intestinal fluid (without enzymes) and in deionized water. If a dissolution specification is to be used as a quality control measure then it must be a sensitive and discriminating indicator of differences in product characteristics. In a telephone conversation on January 28, 1985, the reviewer requested that dissolution be conducted in simulated gastric juice (without enzymes) and buffer (pH 6). The firm felt this data was unnecessary and did not provide the data. However, upon request the firm agreed to provide the pH solubility profile of the parent drug (MK-421). The Division of Biopharmaceutics expresses concern about the proposed dissolution specifications because of the following observations.

a. Only approximately % of the dose administered is absorbed. The capsule formulation used in the investigation by (#523) resulted in % absorption, a value greater than that reported from other studies. A solution was not used as a reference product in any of the bioavailability studies. This was also confirmed in a telephone conversation with the firm (Dr. Alice Till). Of concern is whether or not there is a formulation effect on extent of absorption and the possibility that other formulations (i.e. by another firm) may have greater absorption and result in a substantial difference in clinical response. However, it was learned that unabsorbed drug is primarily MK-422, the product of hydrolysis of MK-421 in the GI tract.

b. The proposed formulation contains $NaHCO_3$. As per the firm, the pH of the dissolution media was not monitored during dissolution studies and a buffer was not used.

4. Data to support the appropriateness of the extrapolation methods used by the firm to remove part of the AUC in studies #6 and #168 was not provided. However, these methods have little impact on the outcome of this review.

5. With respect to the package insert:

a. The package insert states that enalapril is extensively hydrolyzed to enalaprilic acid. Only approximatlly 60% of enalapril absorbed is hydrolyzed to enalaprilic acid. Use of the word "extensively" is misleading.

b. CNS penetration - The statement regarding CNS penetration ("enalapril does not enter the brain") should say that in normally recommended doses CNS penetration is neglible (Refer to comment #7 below). Also, the data is extrapolated to humans from animal studies.

c. In the package insert, the firm should explain the meaning of "effective half-life for accumulation", in contrast to the conventional elimination half-life which is most commonly used and understood by clinicians.

d. The amount or fraction of drug removed during a usual 4 hour hemodialysis run is not stated. It is useful to know if a replacement dose is necessary post hemodialysis. If yes, include the amount.

e. The firm's explanation for the prolonged terminal phase is a hypothesis.

6. The impact of dose on the rate of drug absorption (assessed with Tmax in several studies) can be evaluated by using Enalapril concentrations. Measuring MK-422 will reflect availability(absorption and hydrolysis) of MK-422 and not only absorption of MK-421. Hydrolysis appears to be the rate limiting step for formation of MK-422 from MK-421.

7. Large doses of MK-421 (1.0 mg/kg PO) given repeatedly may result in CNS penetration of MK-422 (Cohen M, Kurz K,; Captopril and MK-421: Stability on storage, distribution to the Central Nervous System, and onset of activity, Federation Proceedings, 42(2):171-175, 1983).

8. It is useful to include in the labelling protein binding values and a statement that the percent drug bound over the concentration range of clinical relevance(^{6}M) ranged from in the equilibrium dialysis and in the ultrafiltration experiment.

The following specific comments refer to the study listed before each section.

#512 - 1. The data suggest that the rate of absorption of MK-421 is faster than the rate of hydrolysis to MK-422.

2. This study only accounts for approximately 85% of the dose administered. Radioactivity found in the urine of subject #2 unaccounted for by MK-421 or MK-422 indicates limited metabolism of one or both of these compounds.

3. The variability in Cmax and AUC for MK-421 is large.

#6 - 1. The renal clearances of MK-422 given in table 3 (refer to table 6-3 in this review) are based on AUC adjusted (extrapolated techniqes employed). Statistical analysis showed a significant difference in clearance with a change in dose (2.5 vs 5 mg). This is consistent with a non-linear process.

2. The Area Under the Serum Concentration vs. Time Curve (AUC) was adjusted by extrapolating the terminal slope to time 0 and subtracting the corresponding AUC from the total AUC (also done in study #168).

#503 - 1. The data for MK-422 is quite variable.

2. MK-521 (L-154,826) is not the subject of this NDA and therefore will not be discussed or evaluated.

3. Based on urinary excretion data, 61% of the dose was absorbed and 43% was available as active drug (MK-422).

#518 - 1. Quality control statistics for MK-739 are given on page 2, in attachment 3 (vol 3.335), however the structure or identity of MK-739 was not given.

2. Subject #3 (wt. 103 Kg) may not be grossly overweight, however, exclusion of the volunteer from the study might have been prudent since he is about 34% above IBW (77 Kg) based on height and fails to meet entry requirments.

3. It was not stated as to whether or not a statistically significant difference in mean percent urinary recovery of MK-422 given in Table 3, page 793, vol 3.335,was observed between treatments. (refer to table 518-5 in this review)

#555 - 1. In the summary table on page 857, vol 3.335, the column heading "Linear Log-dose Response" dose not refer to pharmacological response. It was interpreted as the relationship between the log transformed dose and each parameter measured. Expound on the manipulation and comparison in case of misinterpretatioon.

2. From this study, approximately 50% of the dose is absorbed. The remaining amount is either unabsorbed from the gut (as parent drug or MK-422 or other metabolite) and/or absorbed and undergoes a metabolic conversion prior to systemic availability (first-pass effect). The former is consistent with data from other studies.

3. The urinary data normalized for dose shows a borderline significant difference (P = 0.014) between 2.5, 10 and 40 mg doses [F = 0.28, 0.34, 0.35, respectively]. The dose adjusted AUC decreases significantly (P less than 0.01) with increasing doses of 2.5, 10, and 40 mg [AUC = 630, 423, 361, respectively]. An explanation for this inconsistency was not given, however, it is consistent with saturable protein binding.

#110 - 1. How do the present observations affect dosing recommendations in patients with renal failure?

2. Does the volume of distribution of enalapril and enalaprilic acid change in renal failure?

3. Since the drug was administered 1 hour prior to initiating dialysis the firm is unable to separate variability in absorption of enalapril and/or its hydrolysis to MK-422 from the effect of dialysis as measured in this study.

4. Failure to recover 100% of administered MK-422 equivalents within 48 hours might also be due to incomplete urinary collection of drug. Since MK-422 is primarily renally excreted a substantial increase in half-life is expected in patients with renal impairment. Urinary collection must be conducted for an appropriate length of time.

#168 - 1. It is true that the difference in cumulative urinary data of Total Drug between oral and IV administration of enalapril maleate (urinary data 0.63 vs. 1.0) is related to the absence of an absorption phase (no first-pass effect and/or formulation effect) following IV administration, however, this does not explain the similarity in "availability" of MK-422 for the different routes of administration (0.38 vs. 0.43). It is unclear why the extent of hydrolysis of MK-421 to MK-422 depends on the route of administration (0.6 vs. 0.45).

2. Evaluation of urine vs. serum data shows inconsistent results. Dose adjusted AUC from serum data is significantly different among treatments. In contrast, no significant difference in "availability" of MK-422 was seen in cumulative urinary data.

3. The AUC was adjusted by extrapolating the terminal slope to time 0 and subtracting the corresponding AUC from the total AUC (also done in study #6).

#53 - 1. Statistical power was provided for urinary recovery of MK-422 and Total Drug as percent of administered MK-422 equivalents.

2. AUC was not adjusted by extrapolating the terminal slope to time 0 and subtracting the corresponding AUC from the total AUC as done in previous studies (#6,168).

3. There was no significant difference (P greater than 0.05) between tablets and capsules in Total Urinary Recovery of MK-422. For Total Drug, the power to detect a 20% difference (alpha = 0.05) is 0.65 and to detect a 25% difference is 0.86. 75/75 ratio comparison of Total Urinary Recovery resulted in 72.7% (8/11) within 75-125%.

#523 - 1. The data shows the variability in absorption, extent of hydrolysis and availability (see bioavailability section for comparison of values). There is a tendency for the capsule to be better absorbed, have a greater % hydrolysis and be more available than the tablet but not significantly. Based on urinary recovery of Total Drug (as % of dose given) 78% of the dose is absorbed.

#17 - 1. In calculating statistical power to detect differences between treatments, it was not stated whether or not the mean square of the error term was obtained from ANOVA analysis of log transformed data.

#634 - 1. Blood sampling for digoxin was conducted for a period less than 1 usual half-life of the drug (half-life approximately 40 hours). Use of a nonspecific assay precludes formulating conclusions from the data. The impact of enalapril on the absorption and disposition of digoxin cannot be assessed. In addition, extrapolation of the results of this study to the clinical setting is limited to a single isolated 0.25 mg oral dose of digoxin.

#618 - 1. The firm should have explained the increase in the coefficient of variation observed with increasing plasma concentrations of furosemide obtained from quality control standards analyzed with each run of samples over a 1 month period.

VIII. RECOMMENDATION:

The Division of Biopharmaceutics has determined that the data is acceptable. It is concluded that this submission fulfils the requirements demonstrating the bioavailability and pharmacokinetic disposition of enalapril maleate, the subject of NDA 18-998.

Comments number 5a, c, d and 8 should be forwarded to the firm.

The Division of Biopharmaceutics recommends that dissolution specification be Q % in minutes using USP method II at 50 rpm in 900 ml of water, at 37°C. The firm should use the USP Acceptance Table criteria for this specification.

The firm should forward 300 units of each strength to Dr. V.K. Prasad, Chief of Biopharmaceutics Research Branch, HFN-224, FOB-8, Room 6076, 200 C Street S.W., Washington, D.C. 20204

/S/ 4/18/85

Gene D. Mason, Pharm.D.
Pharmacokinetic Review Branch

RD Initialed by M.Y.Huang, Ph.D.
FT Initialed by C.T. Viswanathan, Ph.D. /S/

cc: NDA 18-998 orig., HFN-110 (2), HFN-226 (Mason), Chron, Division, Drug and Review Files.

GDM/dea/kek/smj/2639x (3/14/85)

Appendix I

Individual Studies

NDA 18-998
Enalapril maleate
Study #512
Wang #2445x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: A 3-way Crossover Study to Determine the Absorption and Metabolic Disposition of ^{14}C -L-154, 826, ^{14}C -L-154, 628, and ^{14}C -L-154,739 in Normal Volunteers

Objective: To characterize absorption and metabolic disposition of a, b, c
a. ^{14}C -L-154,826; MK-521
b. ^{14}C -L-154,628; MK-422
c. ^{14}C -L-154,739; MK-421

Investigator/Site: [redacted]

Design: Open, random assignment, 3-way complete crossover

Dosing: Single 10 mg oral doses of a, b, or c administered as dry-filled capsules after an overnight fast. One week washout between dosing
a. MK-521: 9.32 mg.
b. MK-422: 9.62 mg
c. MK-421: 9.51 mg

Subjects: 6 healthy adult (22-43 year old) male volunteers: Average weight 70 kg; Exclusion Criteria - history of cardiac, renal, or GI disease (including ulcers); habitual drug use or history of drug and/or alcohol abuse; Abnormal prestudy physical exam or laboratory screen (hematology, blood chemistry, urinalysis)

Concomitant Medications: None allowed. No other drug 7 days prior to study. Moderate alcohol consumption allowed except on day 1 of each treatment phase.

Specimens:

a. Blood - 0 (pre-drug), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 72, 96, 120 and 144 hours post dosing

b. Urine (Intervals)
Day 1: 0-2, 2-4, 4-6, 6-8, 8-10, 10-24 hours after dosing

c. Fecal - Days 1-7: 0-24 hours

Analytical Procedure-

Results:

Table I

(mean ± S.D.)

	[14C]-MK-421 Total*	MK-422	[14C]-MK-422	[14C]-MK-521
I. Serum				
C_{max}(ng/ml)	90.4 ± 39.3	59.4 ± 20.3	2.2 ± 1.3	39.0 ± 27.4
t_{max} (hr)	1.6 ± 0.8	3.5 ± 0.5	22.0 ± 14.2	7.0 ± 1.1
$AUC_{0-\infty}$(ng•hr/ml)	---	682 ± 173	199 ± 69	726 ± 306
II. Urine				
% recovery	60	43	3	32
% radioactivity	56.1 ±3.7	---	4.7 ±2.6	27.9 ±16.3
III. Feces				
% radioactivity	(^{14}C)26.9 ±11	---	80.7 ±21.3	55.9 ±15.4
IV. Total % recovery				
% radioactivity	83		85.4	83.8

* Total MK-422 after hydrolysis of MK-421

Statistically significant differences between treatments are given in Table 512-2.

Tables:

Tables 512-3 and 4: contain material balance data for MK-421 and MK-422 respectively

Tables 512-5 and 6: gives individual urine and serum data for MK-421 dosing.

Table 512-7: Individual C_{max} and T_{max} values.

Table 512-8: Individual AUC (infinity) for MK-422 following oral administration of MK-421 and MK-422.

Table 512-9: Thin layer chromatography.

Table 512-9: Urinary and Fecal recovery of radioactivity.

Firm's Conclusion:

1. MK-421 is more rapidly absorbed than MK-422 and MK-521.

2. MK-422 is poorly absorbed after oral administration.

GDM/kek/smj/2445x

NDA 18-998
Enalapril maleate
Study #6
Wang #2547x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: A study to compare the Safety, Tolerance, Humoral Effects and Initial Pharmacokinetics of Single Increasing Intravenous Doses of 2.5, 5 and 10 mg Mk-422 with Placebo in Healthy Male Volunteers.

Objective:

1. To evaluate the effects of sequentially increasing intravenous doses of 2.5 to 10 mg of MK-422 versus placebo
2. To study serum and urine levels of MK-422 after I.V. administration
3. To study the effects of I.V. doses of MK-422 on systolic and diastolic BP in normal volunteers
4. To study the effects of I.V. doses of MK-422 on plasma renin activity, aldosterone and converting enzyme activity.

Investigator/Site:

Design: Double-blind, randomized, 4-way complete crossover. Six day washout period

Dosing: Single doses of MK-422 (L-154,628) given intravenously; 2.5, 5, 10 mg versus placebo (sterile sodium chloride for injection); subjects fasted overnight

Subjects: 12 healthy adult (20-36 year old) male volunteers within ± 10% of their ideal body weight according to Metropolitan Life Insurance Company, Statistical Bulletin #40, 1959; Inclusion Criteria: Normal medical history, clinical laboratory screen (hematology, blood chemistry, urinalysis), physical exam and EKG; Exclusion Criteria: Hypertension, cardiovascular, renal or hepatic disease, abnormal BUN, and medications within 2 weeks of study or any investigational drugs 3 months prior to study.

Concurrent Medications: None allowed

Specimens:

a. Serum - 0, 10 min., 20 min., 30 min., 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72 hours

b. Urine (intervals): -1 to 0, 0 to 1, 1-2, 2-4, 4-6, 6-8, 8-24, 24-36, 36-48, 48-72, 72-96, 96-120 hours

Analytical Procedure:

In-Vivo Results:

Pharmacokinetic Parameters(MK-442)-Mean + Standard Deviation

	2.5 mg	5 mg	10 mg	Comparisons
Terminal Slope (hr^{-1})	0.0189 ±0.0036	0.0195 ±0.0034	0.0192 ±0.0041	NS
Urinary recovery as MK-422 (% of dose)	92±10	96±7	93±9	NS
Renal clearance (ml/min.)	137±28	155±30	152±28	5 mg > 2.5 mg $p < 0.05$
*AUC^E(extrapolated) (ng•hr/ml)	105±28	100±24	120±23	10 mg >> 2.5, 5 mg $p < 0.01$
AUC_0^∞ (ng • hr/ml)	379±79	639±93	1203±193	---
$AUC_0^\infty - AUC^E$	274±40	538±80	1082±181	---

*AUC^E: AUC extrapolated from terminal slope to 0 time.

Statistics: Comparison of treatments were analyzed using an analysis of variance for a 4-way crossover design.

Tables:

Table 6-1: Individual AUC values for 2.5, 5.0 and 10 mg doses.

Table 6-2: Individual urinary recoveries of MK-422.

Table 6-3: Individual renal clearances for MK-422.

Table 6-4: Mean serum concentrations of MK-422.

Table 6-5: Individual terminal slopes of MK-422 serum profiles.

Table 6-6: Individual serum concentrations of Mk-422.

Table 6-7: mean serum concentration vs. time profile.

Table 6-8: Individual urinary excretion of MK-422.

GDM/kek/smj/2547x

NDA 18-998
Enalapril maleate
Study #503
Wang #2449x

Merck Sharp and Dohme
Submission date:
January 31, 1984

Title: An Open, Randomized, Three-way, Crossover Study in Normal Volunteers to Study the Bioavailability of L-154,739 (MK-421), L-154,628 and L-154,826

Investigator/Site: [redacted]

Objective:

a. to determine the bioavailability of single oral doses of L-154,739 (MK-421) and L-154,826 (MK521).
b. to evaluate the safety and tolerability of MK-421 and MK-521.
   Note: The protocol originally specified a three-way crossover but was subsequently amended to include only MK-421 and MK-521.

Design: Open, randomly assigned, two-way complete crossover.

Dosing: Single oral 10 mg dose (capsule); One week washout period; subjects fasted 12 hours prior to dosing.

Subjects: 12 healthy adult (22-33 year old) male volunteers with proportionate weight and height; Inclusion Criteria: Normal pre-study laboratory screen (hematology, blood chemistry, Urinalysis); Exclusion Criteria: history cardiac, renal, or GI (including Ulcers) disease, history of drug or alcohol abuse.

Concomittant Medications: None allowed.

Specimens:

Blood- 0, 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, and 72 hours postdrug.

Urine (Intervals)- 0 to 24, 0-2, 2-4, 4-6, 6-8, 8-10, 10-24, 24-48, 48-72 hours postdrug.

Fecal (Intervals)- 0-24, 24-48, and 48-72 hours postdrug.

Analytical Procedures:

[redacted]

Results:

Pharmacokinetics

	Serum (mean ±S.D.)				Urine	
	Cp^{max} (ng/ml)	t_{max} (hr)	$\bar{t}1/2$ (hr)	AUC_0^{72hr} (ng hr/ml)	% Recovery ($\bar{p}$ 72 hrs)	Clr ml/min
MK-422*	40.5 ±17.5 (CV 43.2%)	4(3.75**)	35	490 ±152.2 (CV 31.1%)	43	158
Total Drug	59.0 ±21.5	1.2		----	61	--
MK-521	38.4 ±22.3 (CV 58.1%)	7	30	687 ±327.8 (CV 47.7%)	29	106

*MK-422 = Active diacid of MK-421
**Calculated from data in Table IV, Attachment 3 in vol. 3.334.

Tables:

Table 503-1: Individual C_{max} and T_{max} for MK-421 and MK-422

Table 503-2: Individual AUC (0-72 hrs.) for MK-422

Table 503-3: Individual urinary recovery as % of administered dose

Table 503-4: Individual Renal clearances of MK-422

Table 503-5: Individual serum concentrations of Total Drug as MK-422

Table 503-6: Individual serum concentrations of MK-421

Table 503-7: Individual serum concentrations of MK-422

Table 503-8 and 8: urinary excretion of MK-422 and Total Drug

Figure 503-1: Mean serum concentration vs. time profile of MK-422

GDM/dea/kek/smj/2449x (10/9/84)

NDA 18-998
Enalapril Maleate
Study: #518
Wang #2451x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: An open study to determine the steady-state kinetics of repeated Single Oral Doses of MK-421 in normal voluteers.

Investigator/Site:

Objective:
1. To determine the serum profile, accumulation, and urinary excretion of MK-422 (L-154,628)

Design/Dosing: Open study; single daily oral 10 mg doses (capsule) of MK-421 x 7 days; subjects fasted overnight.

Subjects: 12 healthy adult (18-30 YO) male volunteers proportionate for height and weight; normal prestudy laboratory screen (Hematology, Blood Chemistry, Urinalysis), physical exam and EKG; Exclusion criteria - previously taken captopril, history of cardiac, renal or GI disease and history of drug use and/or alcohol abuse

Concurrent Medications: None

Specimens:

Day 1 (Inpatient)
Blood: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 (just before next dose) hours.
Urine (Intervals): -1 to 0, 0-1, 1-2, 2-4, 4-8, 8-12, 12-24 hours.

Days 2-6 (outpatient)
Blood - 0 (predrug) hour
Urine - 0-24 hours

Day 7 (Inpatient) and Day 8-11 (Outpatient)
Blood - 0 (predrug), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 36, 48, 60, 72 and 96 hours.
Urine (Intervals): 0 to 1, 1-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours

Analytical Procedures:

Results:

Table 518-1: Individual serum concentrations and AUC of MK-422 from 0-24 hrs. after dose 1.

Table 518-2: Individual serum concentration and AUC of MK-422 from 0-24 hrs. after dose 8.

Table 518-3: Individual urinary recovery (over 24 hrs.) of MK-422 for days 1-8.

Table 518-4: Individual minimum serum concentrations of MK-422 24 hours post administration on days 1-8.

Table 518-5: Individual urinary recovery (as % of dose) of MK-422.

Table 518-6: Urinary excretion of MK-422 on day 8 only.

Figure 518-1: Mean MK-422 serum profiles on days 1 and 8; and C_{min} on days 2-8.

Firm's Conclusion:

Steady state exists by the third or fourth dose of MK-421 and there is little accumulation of MK-422 following 8 daily doses.

GDM/dea/kek/smj/2451x

NDA 18-998-Enalapril Maleate
Study #555
Wang #2457x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: A Double-Blind, Single-Dose, 4-Period, Crossover Study in Normal Volunteers to Determine the Effect of Dose on the Kinetics of MK-0421(L-154,739)

Investigator/Site: [redacted]

Objective: To determine the effect of dose (2.5 to 40 mg, P.O.) on pharmacokinetic disposition of MK-421

Design: Double-blind, 4-way, randomly assigned, complete crossover.

Dosing: Single oral doses (capsules) of MK-421 (2.5, 10, 40 mg); MK-422, 5 mg IV; overnight fast; ten day washout periods

Subjects: 13 healthy adult (20-34 year old) male volunteers were entered, however only 12 completed the study. Inclusion Criteria: Height proportional to weight, normal prestudy laboratory screen (hematology, blood chemistry, urinalysis), PExam and ECG. Exclusion Criteria: previously taken Captopril, history of cardiac, renal or GI disease, history of drug use and/or alcohol abuse, multiple and/or severe allergies.

Concurrent Medications: None allowed.

Specimens: Blood- 0 (predrug), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours for oral dosing; 0 (predrug), 10 mins., 20 mins, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours for IV dosing
Urine (intervals): -1 to 0, 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120 hours.

Analytical Methods: [redacted]

Results:

	MK-0421 2.5 MG P.O		MK-0421 10 MG P.O.		MK-0421 40 MG P.O.		Linear LOG-DOSE RESPONSE
	N	MEAN	N	MEAN	N	MEAN	
Ratio of MK-0422/total drug for total urinary recovery[a,b] geometric means	11	0.58	11	0.62	10	0.65	p=.06
Bioavailability of MK-0422[a,b,c] (MK-0422 urinary recovery P.O. /I.V.)	10	0.28[d]	10	0.34[d]	9	0.35[d]	p=.014
Absorption of drug[a,b,c] (urinary recovery total drug P.O./MK-0422 I.V.)	10	0.48[d]	10	0.55[d]	9	0.54[d]	p>.2
MK-0422 $AUC_{0-\infty}$(ng hr/ml) (dose-adjusted relative to 10 mg capsule; subtraction of extrapolated area not done)	12	630		423		361	p<.01
Based on 2.5 mg capsule		158		106		90	
MK-0422 C_{max} (ng/ml) (dose-adj)	12	23.5		32.3		37.4	p<.01
MK-0422 t_{max} (hours)	12	6.50		3.92		3.33	p<.01
Enalapril C_{max} (ng/ml) (dose-adj)	12	70.8		71.0		74.8	p>.2
Enalapril t_{max} (hours)	12	0.96		0.92		0.79	p=.03

[a]AN 4-Excluded due to apparently incomplete urine collections
[b]AN 11-Had missing data for the 40 mg dose
[c]AN 2-Excluded because 123% recovery after I.V.
[d]Geometric means

Tables:

Table 555-1: Individual C_{max} and T_{max} of MK-421 following oral dosing

Table 555-2: Individual Individual C_{max} and T_{max} of MK-422 following oral dosing

Table 555-3: Individual AUC (0-infinity) for MK-422 and Ratios of AUC

Table 555-4: Individual extrapolated AUC values obtained with IV dosing

Table 555-5: Individual total urinary recovery of Total Drug

Table 555-6: Individual total urinary recovery of MK-422

Table 555-7: Mean serum concentration vs. time profile for MK-422

Table 555-8: Mean AUC for MK-422 versus F Dose with and without extrapolation techniques

Table 555-9: Individual ratio of MK-422/Total Drug for total urinary recovery

Firm's Conclusions:

a. The extent of absorption of enalapril is similar for capsules containing 2.5, 10 and 40 mg enalapril maleate

b. Hydrolysis and bioavailability of enalapril are similar for 10 and 40 mg, but slightly less for 2.5 mg

c. The disposition of MK-0422 appears to be nonlinear, as evidenced by the less than proportionate increases in $AUC_{0-\infty}$, greater than proportionate C_{max} for MK-0422 and decreases in T_{max} for MK-0422 with increasing doses of enalapril maleate

GDM/kek/smj/2457x

NDA 18-998
Enalapril Maleate
Study #110
Wang #2478x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: An Acute, Single Dose Study to Evaluate Safety and Tolerance and Determine Serum Profiles and Urinary Excretion of Oral Enalapril Maleate (10 mg) in Patients with Chronic Renal Disease Compared to that in Normal Volunteers

Investigator/Site:

Objective:

1. To evaluate the effect of renal failure on the pharmacokinetic disposition of enalapril maleate after a single dose
2. To investigate the clearance of enalapril maleate and enalaprilic acid during hemodialysis

Design: 2 treatment periods; a. no dialysis b. dialysis
3 groups of subjects:
Group 1: 10 patients with creatinine clearance ≤ 3 ml/min.
Group 2: 9 patients with creatinine clearance 10-79 ml/min.
Group 3: 9 volunteers with creatinine clearance ≥ 80 ml/min.
Single dose, open design

Dosing: Treatment Period I (All Subjects): 10 mg of enalapril maleate given orally under fasting conditions.
Treatment Period II (Patients in Group 1 only):
10 mg of enapril maleate given orally 1 hour prior to a 4 hour hemodialysis run; fasting conditions.
Two week interval between treatments.

Subjects: 19 male and 9 female patients and volunteers. 4 subjects over 70 years of age failed to meet criteria for inclusion (over age of legal consent to under 70 years old) but were included because all other criteria were met.

Specimens:

Treatment Period I

Blood (all groups) - 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hours after dosing
Urine (Groups 2 & 3) - 0 to 4, 4-8, 8-12, 12-24, and 24-48 hours post dosing.

Treatment Period II

Blood (Group 1) - 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 and 48 hours after dosing.

Analytical Procedures:

Results:

Effect of Renal Failure

Mean AUC (0-48 hrs) ± S.D.
(ng•hr/ml)

Normal	409 ± 96
Mild to Moderate	1986 ± 1430 (sig normal, $p < 0.01$)
Moderate only	2497 ± 1267 (sig normal, $p < 0.01$)

Mean Urinary Excretion Rate (ug/hr)

	0-4		4-8		8-12		12-24		24-48	
	EA	TD	EA	TD	EA	TD	EA	TD	EA	TD
Normal	186	545	228	251	122	127	39	39	6.8	6.8
Mild - Mod	55**	168**	112**	140**	80	87	63	63	17	17
Mod	24**	77**	94**	124**	78	87	69*	69*	20*	20*

*, ** significantly different from normals, $p < 0.05$, $p < 0.01$, respectively
EA = Enalaprilic Acid; TD = Total Drug

48-hour Urinary Recovery (% of dose administered in terms of Enalaprilic Acid)

	EA	TD	EA/TD
Normal	40 ± 5	62 ± 8	0.64
Mild-Mod	30 ± 13	38 ± 17**	0.82**
Mod	30 ± 15	35 ± 19**	0.89**

** Significantly different from normals, $p < 0.01$

Medium AUC (0-6 hours) During Dialysis (hours 1-5)
(Enalaprilic Acid plasma curve following
Enalapril Maleate Administration)

I. Without Dialysis	319 ng hr/ml
II. With Dialysis	149 ng hr/ml (sig lower than I, $p < 0.01$)

Tables:

Figure 110-I: Mean serum concentration profiles of Enalapric Acid

Table 110-1: Individual AUC (0-6 hrs.) for enalaprilic acid with and witout dialysis in severe renal failure

Table 110-2: Individual AUC (0-48 hrs.) for enalaprilic acid in normals and patients with mild to moderate renal insufficiency

Table 110-3: Individual urinary recovery (0-48 hrs.) of enalaprilic acid and Total Drug in normals and patients with mild to moderate renal insufficiency

Table 110-4 and 5: Individual urinary excretion rates of enalaprilic acid and Total Drug

Firm's Conclusion:

A. Impaired renal function results in elevated serum/plasma concentrations of enalaprilic acid following administration of enalapril maleate.

B. Mild to moderate renal impairment causes a decrease in the excretion rates of enalaprilic acid and enalapril, with an apparent increase in the extent of conversion of enalapril to enalaprilic acid (and/or an increase in non-renal elimination of enalapril other than metabolism to enalaprilic acid) compared to normals.

C. Enalaprilic acid is dialyzable in patients with severe renal impairment.

GDM/dea/kek/smj/2478x (9/27/84)

NDA 18-998
Enalapril Maleate
Study #168
Wang #2479x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: A Double-Blind, Single-Dose, Six-Period Crossover Study in Normal Volunteers to Determine the Bioavailability of 5, 10, 20 and 40 mg Tablets of Enalapril Maleate Utilizing an Enalaprilic Acid (E.A.) (MK-422) and an Enalapril Maleate (E.M.)(MK-421) Intravenous Standard

Investigator/Site: [redacted]

Objective:
To determine the bioavailability of enalapril maleate tablets (5, 10, 20, 40 mg) when compared to an intravenous standard of enalapril maleate (5 mg) and enalaprilic acid (5 mg).

Design:
Double-blind (with respect to oral doses), random assignment, six-period complete crossover.

Dosing: Single dose; fasting conditions; six day washout period;
treatments:
a. EM 5 mg tablet P.O.
b. EM 10 mg tablet P.O.
c. EM 20 mg tablet P.O.
d. EM 40 mg tablet P.O.
e. EA 5 mg I.V.
f. EM 5 mg I.V.

Subjects:
12 healthy adult (19-33 year old) male volunteers within ± 10% of IBW entered the study. Subject #10 was greater than approximately 20% of IBW and was included in the study for unexplained reasons. Two subjects voluntarily withdrew from the study. Data from Subject #6 was not analyzed because of markedly consistent differences from other subjects. Exclusion Criteria: history of cardiac, renal, GI disease, multiple allergies, history of alcohol and/or drug abuse, and WBC 4.0×10^3 per mm^3 or urinary protein 500 mg per 24 hours.

Concurrent Medications: None allowed

Specimens:

Blood - E.A. and E.M. (IV): 0, 10 min, 20 min, 30 min, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours.
E.M. (Oral): 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours.
Urine (intervals) - All treatments: -1 to 0, 0-1, 1-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96 hours.

Analytical Procedures: (

)

Results

Table I Cumulative Urinary Data

	E.M. Tablets				E.M.-IV	ANOVA
	5mg	10mg	20mg	40mg	5mg	(tablets)
Bioavailability[1]						
Geometric Mean	0.38	0.44	0.38	0.36	0.43	N.S. (>.2)
(C.V.)	(28.2)	(20)	(28.2)	(29.7)	(13.9)	
Absorption[2]						
Geometric Mean	0.63	0.73	0.62*	0.59*	(1.0)	0.06
(C.V.)	(23.4)	(20.3)	(28.1)	(26.2)		
Extent of Hydrolysis[3] of Enalapril to E.A.						
Geometric Mean	0.60	0.61	0.62	0.61	.45	N.S
(C.V.)	(8.3)	(9.8)	(10.6)	(9.8)		

* significantly different from 10 mg dose, $p < 0.05$

1. As estimated from the dose-adjusted urinary recovery ratio of E.A. for the E.M. formulations to E.A. IV
2. As estimated from the dose-adjusted urinary recovery of total drug (E.A. measured after hydrolysis) from E.M. tablets to total drug from enalapril maleate I.V.
3. Estimated from the ratio Bioavailability/Absorption (or urinary MK-422 ÷ Total Drug in urine)

Table II - Mean AUC 0-∞ (ng hr/ml) for E.A.

	E.M. Tablets				E.M.-IV	E.A.-IV
	5mg	10mg	20mg	40mg	5mg	5mg
Mean AUC[1]	255	440	731	1331	270	652
(C.V.)	(11.3)	(9.4)	(16.7)	(18.7)	(23.2)	(14.6)
Dose Adjusted to 5 mg						
	255	220	183*	166*,**	270	652

* significantly less than 5 mg; $p < .01$
** significantly less than 10 mg; $p < .05$
1 - Areas not adjusted by extrapolation techniques.

Table III- Cpmax & tmax for Enalaprilic Acid

	E.M. Tablets				E.M.-IV
	5mg	10mg	20mg	40mg	5mg
Cp^{max} (ng/ml)	15.3	37.4	70.8	123.1	16.5
(C.V.)	(41)	(45)	(48)	(34)	(27)
Cp^{max} (ng/ml)-dose adjusted*	15	19	18	15	16
t^{max}	4.8	3.9	3.2**	3.4**	4.0

* No significant differences
** Significantly less than 5 mg; p 0.05

Tables:
Table 168-4: Individual C_{max} and T_{max} for enalaprilic acid

Table 168-5: Individual AUC (0-infinity) for enalapril acid

Table 168-6: Individual values of absorption following oral enalapril maleate.

Table 168-7: Individual values of "Bioavailability" (avaiability of active drug)

Table 168-8: Individual values of extent of hydroloysis of enalapril to enalaprilic acid

Table 168-9 and 10: Urinary recovery of Total Drug and enalaprilic acid

Table 168-11 and 12: Statistical analysis (ANOVA) of serum and urine data

Firm's Conclusion:

1. The "bioavailability" of enalaprilic acid is similar for 5, 10, 20 and 40 mg Enalapril Maleate tablets.

2. The bioavailability of enalaprilic acid from I.V. enalapril maleate is similar to that for the oral tablets. The mean extent of hydrolysis of enalapril to enalaprilic acid however, is approximately 30% less than that for the tablets (see urinary data). The difference in bioconversion between oral and IV administration of enalapril maleate likely reflects first-pass bioconversion following oral administration.

GDM/dea/kek/smj/2479x (3/14/85)

NDA 18-998
Enalapril Maleate
Study #53
Wang #2482x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: A Study to Determine the Bioavailability of MK-421 Capsules (10 mg) and MK-421 Tablets (10 mg) Using MK-422 Intravenous (5 mg) as a Standard

Investigator/Site: [redacted]

Objective: To determine the BA of MK-421 tablets and MK-421 capsules using MK-422 I.V. as a standard.

Design: Open, randomized, single-dose, complete crossover.

Dosing: MK-421 tablet, 10 mg, P.O. vs.
MK-421 capsule, 10 mg, P.O. vs.
MK-422 I.V., 5 mg.
13 day washout period; fasting 8.5 hours ante and 3 hours post dosing.

Subjects: 12 healthy normotensive adult (23-33 year old) male volunteers within ± 10% IBW. Subjects were judged to be healthy based on medical history, PE, EKG and laboratory data (hematology, blood chemistry, urinalysis) Exclusion criteria: history of allergies, cardiac, renal or GI disease, history of drug/alcohol abuse, WBC 4.0 x 10^3 per mm^3, total urinary protein 500 mg per 24 hours.

Concurrent Medications: None allowed; no other drugs for 7 days prior to initiation and until completion of the study.

Specimens:
Blood
I.V. Dosing - 0, 10 mins, 20 mins, 30 mins, 1, 1.5, 2, 4, 6, 8, 12, 24, 48 and 72 hours.
Oral Dosing - 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours

Urine (intervals): -1 to 0, 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 hours.

Analytical Methods:

[redacted]

Results:

Table 53-1: Mean values for parameters derived from serum and urine data

Table 53-2: Statistical power for urinary recovery data

Table 53-3: Individual and mean C_{max} and T_{max} of MK-421 in serum

Table 53-4: Individual and mean C_{max} and T_{max} of MK-422 in serum

Table 53-5: Individual and AUC (0-72 hrs.) of MK-422

Table 53-6: Individual and mean urinary recovery ratios of MK-422 to Total Drug

Table 53-7: Individual and mean serum concentrations of MK-422 after oral dosing

Table 53-8: Individual and mean serum concentrations of MK-422 after IV dosing

Figure 53-1: Mean MK-422 serum profile following oral administration of tablets and capules.

There were no statistically significant ($p < 0.05$) differences between tablets and capsules in, the following parameters;

a. Cp^{max}, tpk for serum concentrations of MK-422 & MK-421,

b. Urinary recovery of MK-422, total drug (MK-422 + MK-421), or

c. Urinary recovery ratio of MK-422 to total drug.

Statistical power analysis is given in table 53-2.

Firm's Conclusions:

1. Based on urinary recovery of MK-422 and total drug, the bioavailability of MK-422 following MK-421 tablets and capsules is the same in healthy volunteers.

GDM/dea/kek/smj/2482x (3/14/85)

NDA 18-998
Enalapril Maleate
Study #523
Wang #2483x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: An Open, Single-Dose, 2 period, Crossover Study in Normal Volunteers to Determine the Bioavailability of MK-421 Capsules

Investigator/Site: [redacted]

Objective: To determine the bioavailability of MK-421 capsules relative to MK-422 I.V.

Design: Open, randomly assigned, single-dose, two-period complete crossover

Dosing: 10 mg MK-421 capsule P.O. vs.5 mg MK-422 I.V.
2 week interval between treatments; Fasting conditions prior to dosing (since midnight) and for 3 hours after dosing.

Subjects: 12 healthy adult (23-50 year old) male volunteers, neither grossly overweight nor underweight. Subjects were free of cardiac, renal and GI disease by history, PE and laboratory data. Exclusion criteria: regular drug use, history of drug/alcohol abuse or previous use of captopril.

Specimens:

Blood;

Oral - 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post dosing.
I.V. - 0, 10 min., 20 min, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48 and 72 hours post dosing

Urine (Intervals); -1 to 0, 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours post dosing

Analytical Procedures:

[redacted]

Results:

	Mean	95% Conf. Int.
Cp max MK-422 after Caps	42 ng/ml	(34,50)
tmax	3.6 hrs	(3.3, 3.9)
Cp max Total Drug after Caps	66 ng/ml	(58,74)
tmax	1.0 hrs.	(0.6, 1.4)
Urinary Recovery of MK-422 (as % of dose given)		
after I.V.	107 %	(101, 113)
after Caps	56%	(49, 63)
Of Total Drug after Caps	78%	(71, 85)
Ratio of Urinary Recovery (Caps to I.V.)		
of MK 422	0.54[a]	(0.47, 0.62)[b]
of Total Drug	0.74[a]	(0.67, 0.82)[b]

a. geometric mean
b. calculated from $\log_{10}$ of values and converted back

AUC 0 to infinity for MK-422 (ng•hr/ml)

Treatment	# Subjects	Mean	STD	Range
I.V.	10[a]	794	151	
I.V.	9[b]	750	62	
Caps	12	497	81	

a. data for subjects 2 and 6 did not permit calculation of slope of AUC
b. Omitting data from subject 11 whose value, 1192, was greater than 2.6 standard deviations from the mean

Tables:
Table 523-1: Individual and mean C_{max} and T_{max} for MK-422

Table 523-2: Individual and mean AUC (0 - infinity) for MK-422

Table 523-3: Individual and mean ratios of urinary recovery of MK-422 and Total Drug for oral vs. IV administration

Table 523-4: Individual and mean urinary recovery of MK-422 and Total Drug for oral vs. IV administration.

Firm's Conclusion:
1. Base upon urinary recovery ratios, the mean bioavailability of MK-422 from MK-421 capsules is approximately 54%, and the mean absorption of the capsule is approximately 74%.

GDM/dea/kek/smj/2483x (3/14/85)

NDA 18-998
Enalapril Maleate
Study #27
Wang #2484x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: An Open, Single-Dose, Two-Period, Crossover Study in Normal Volunteers to Determine the Bioavailability of MK-421 Tablets.

Investigator/Site:

Objective: To determine bioavailability of MK-422 from MK-421 tablets using I.V. MK-422 as a standard.

Design: Open, randomized, single dose, 2-way crossover.

Dosing: MK-421,10 mg tablet (proposed marketed formulation)
MK-422,5 mg I.V.
AM dosing with fasting since midnight; two week washout period between treatments.

Subjects: 12 adult (23-34 year old) male volunteers judged healthy by medical history, PE and laboratory testing (hematology, blood chemistry, urinalysis, EKG) and within ± 20% of IBW. Exclusion criteria: history of captopril use, cardiac, renal or GI disease, history of drug/alcohol abuse.

Concurrent Medications: None allowed.

Specimens:
Blood;
Oral - 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post dosing. I.V.: 0, 10 mins., 20 mins., 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48 and 72 hours post dosing from the arm opposite that used for injection.

Urine (Intervals): -1 to 0, 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-100 hours.

Analytical Procedures:

Results:

Parameter	Treatment	Mean + SD	95% Confidence Interval
AUC for MK-422 (ng•hr/ml)	I.V.	781 ± 160	(680, 883)
	Tablet	438 ± 110	(368, 508)
Cp^{max} for MK-422 (ng/ml)	Tablet	35 ± 20	(22, 48)
tmax for MK-422	Tablet	3.9 ± 1.1	(3.2, 4.6)
Cp^{max} for Total Drug	Tablet	66 ± 21	(52, 80)
tmax for Total Drug	Tablet	1.1 ± 0.5	(0.8, 1.4)
Urinary Recovery (% of administered MK-422 equivalents)	I.V.	95 ± 7.8	(90, 100)
	Tablet-MK-422	41 ± 16	(30, 52)
	Tablet-Total Drug	58 ± 16	(48, 69)
Urinary Recovery Ratio MK-422	Tablet/I.V.	0.40**	(0.30, 0.54)
Total Drug	Tablet/I.V.	0.59**	(0.47, 0.73)
Terminal Slope (hr^{-1})	IV	0.0129 (half-life = 53.7 hrs.)	
	Tablet	0.0161 (half-life = 43.0 hrs.)	

* statistical tests for normality of the data indicate that the 95% confidence limits may not be exact.
** Geometric Mean

Tables:
Table 27-1 and 2: Individual and mean serum concentrations of MK-422 and Total Drug for oral administration

Table 27-3: Individual and mean serum concentrations of MK-422 for IV administration

Table 27-4: Individual and mean C_{max} and T_{max} for oral tablets

Table 27-5: Individual and mean AUC (0-infinity) of MK-422 for oral and IV dosing

Table 27-6: Individual and mean urinary recovery of MK-422 and Total Drug for oral and IV dosing

Table 27-7: Ratios of urinary recovery of MK-422 and Total Drug

Firm's Conclusions:

1. Based on urinary recoveries of MK 422 and total drug, the bioavailability of MK-422 from the tablet formulation is 40% compared to the I.V. preparation. Absorption of total drug from the tablet is 59% compared to the I.V. preparation.

GDM/dea/kek/smj/2484x

NDA 19-998
Enalapril Maleate
Study #23
Wang #2496x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: An Open Two-Way Crossover Comparison of the Influence of Food on the Single Dose Kinetics and Pharmacodynamics of MK-421 (Given in Its Market Image) in Healthy Volunteers (Lot #X0421-OCT-006-E01)

Investigator/Site:

Objective: To assess the effect of food on the rate and extent of absorption of MK-421

Design: Open, randomized, single dose; two-way crossover design

Dosing: 40 mg MK-421 (tablet), orally under fasting conditions (midnight of previous night) vs. 40 mg MK-421 orally, immediately after a standardized breakfast (1 egg, 2 toast, 5 g margarine, 20 g orange marmalade or jelly, 2 bacon or 2 sausage, 150 ml low fat milk or 100ml orange juice, tea or coffee); there was a 7-day washout period between treatments.

Concomitant Medications: None allowed (including aspirin and alcohol) beginning one week prior to study until its termination.

Subjects: 12 healthy, normotensive, adult (19-32 year old) male volunteers within ± 10% of ideal body weight (according to the Metropolitan Life Insurance Company Statistical Bulletin #40 November - December, 1959) and judged to be in good health based on medical history, P.E., laboratory data (hematology, blood chemistry, urinalysis) and EKG. Exclusion criteria: drug allergies, history of GI, cardiovascular, hepatic or renal disease, history of alcohol abuse, use of investigational drugs 3 months prior to study, WBC 4.8 x 10^3/cu mm., urinary protein 150 mg/24 hrs, positive pregnancy test and use of oral contraceptives.

Specimens:
Blood - 0, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dosing
Urine (intervals): -1 to 0, 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120 hours.

Analytical Procedures:

Results:

Mean and Standard Deviation of Serum and Urine Parameters

	Fasting	N	Food	N	Comparison
Tpk (hr) of MK-422	3.3 ± 0.5	12	3.4 ± 0.5	11[a]	NS
Cp^{max} (ng/ml) of MK-422	153.6 ± 39.1	12	146.6 ± 36.4	12	NS
AUC 0 to 24 hrs for MK-422 (ng• hr/ml)	1208.6 ± 202.7	12	1172.8 ± 211.8	12	NS
AUC 0 to LSC[b] for MK-422 (ng•hr/ml)	1303.8 ± 240.2	12	1261.7 ± 219.9	12	NS
Urinary Recovery: (% administered MK-422 equivalents)					
MK-422	30.5 ± 7.5	11[b]	31.6 ± 8.8	11[c]	NS
Total Drug	53.1 ± 10.1	11	57.6 ± 12.4	11	NS

Geometric Mean

	Fasting	n	Food	n	Comparison
Ratio of MK-422/Total Drug (Based on Total Urinary Recovery)	0.56	11[b]	0.54	11	NS

NS= no significant differences
LSC= last serum concentration
a. subject #2 was omitted because his value was more than 2.6 standard deviations from the mean
b. incomplete urine collection for subject 2
c. incomplete urine collection for subject 5
d. no sample or unable to quantify drug

The power of detecting differences at alpha = 0.05 significance level for urinary recovery of MK-422 and Total Drug as percent of a administered MK-422 equivalents is given below.

	Detectable Difference				
	10%	15%	20%	25%	30%
MK-422	0.5	0.55	0.82	0.96	0.99
Total Drug	0.5	0.55	0.81	0.96	0.99

Tables:

Table 23-1: Individual and mean urinary recovery of MK-422 and Total Drug

Table 23-2: Individual and mean ratio of MK-422/Total Drug for urinary recoveries

Table 23-3 and 4: Individual and mean ratio of MK-422/Total Drug for fractional urinary recovery to 24 hours under fasting and eating conditions.

Table 23-5: Individual and mean AUC of MK-422 over 24 hours for fasting and eating conditions.

Figure 23-1: Mean MK-422 serum profiles under fasting and eating conditions

Firm's Conclusion:

The serum and urine parameters for MK-422 and Total Drug are similar following administration of MK-421 tablets with and without food. Food does not appear to significantly alter the rate and extent of absorption of MK-421.

GDM/dea/kek/smj/2496x (10/3/84)

NDA 18-998
Enalapril Maleate
Study #17
Wang #2530x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title:
A Double-Blind, Crossover Study to Determine the Effect on Bioavailability of MK-421 and Hydrochlorothiazide (HCTZ) Given Alone and Concomitantly to Normal Adults

Investigator/Site:

Objective:
To Assess the effet of concomitant administration of HCTZ and MK-421 on the bioavailability of either preparation when given in single and multiple doses.

Design: Double-blind, randomized, three-way balanced crossover design

Dosing: (MK-421, Capsule)

Days 1-3	Days 4-10	Day 11
	TREATMENT A	
	A.M.	
2 Capsules Placebo	1 Capsule MK-421 10 mg 1 Capsule Placebo	1 Capsule MK-421 10 mg 1 Capsule HCTZ 25 mg
	P.M.	
2 Capsules Placebo	1 Capsule MK-421 10 mg 1 Capsule Placebo	
	TREATMENT B	
	A.M.	
2 Capsules Placebo	1 Capsule HCTZ 25 mg 1 Capsule Placebo	1 Capsule HCTZ 25 mg 1 Capsule MK-421 10 mg

P.M.

2 Capsules Placebo — 1 Capsule HCTZ 25 mg
1 Capsule Placebo

TREATMENT C

A.M.

2 Capsules Placebo — 1 Capsule MK-421 10 mg — 2 Capsules Placebo
1 Capsule HCTZ 25 mg

P.M.

2 Capsules Placebo — 1 Capsule MK-421 10 mg
1 Capsule HCTZ 25 mg

Breakfast, lunch and dinner were respectively at approximately 1030, 1330 and 1830 hours; BID doses were given at 0830 and 2030; There was a 10-day washout period between treatments.

Subjects:
12 healthy normotensive adult (23-41 year old) male volunteers within ± 10% of the ideal body weight and judged healthy on the basis of medical history, P.E., EKG and laboratory data (hematology, blood chemistry, urinalysis). Exclusion criteria: drug allergies, history of GI, cardiovascular, hepatic or renal disease, WBC 4,800/cumm, history of skin rash or proteinuria (150 mg/24 h) or alcoholism, consumption of investigational drugs within three months prior to study.

Concomitant Medications:
Other than study medications, none allowed beginning 7 days prior to study (except occasional use of analgesics) until the end of the study.

Specimens:

Blood- 0, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours on days 4, 10 and 11 for treatments A and B, and on days 4 and 10 for treatment C.

Urine (intervals): -1 to 0, 0-1, 1-2, 2-4, 4-6, 6-8, 8-12 and 12-24 hours on days 4, 10 and 11. In addition, 0-24 hour collections were otained on days 5, 6, 7, 8, 9, 12, 13, 14 and 15.

Analytical Procedures:

Results:

I. Steady State Urinary Recovery (% of dose)

	HCTZ alone (TxB) day 10		HCTZ + E.M. (TxC) day 10	
	0-12	12-24 hrs.	0-12	12-24 hrs.
Mean Urinary Recovery				
HCTZ	77	52	68	44

	E.M. alone (TxA) day 10		E.M. + HCTZ (TxC) day 10	
	0-12	12-24 hrs.	0-12	12-24 hrs.
Mean Urinary Recovery*				
MK-422	45	30	46	27
Total Drug	64	44	63	44

* Expressed as % of MK-422 equivalents administered

The power of detecting a 25 pct. difference between MK-421 alone (or hydrochlorothiazide alone) and the combiniatin treatment in the steady state urinary recovery of MK-422, total drug and hydrochlorothiazide was greater than 0.99.

II. Average* Steady State Urinary Recovery (% of dose)

	E.M. alone (TxA)	HCTZ alone (TxB)	Combo (TxC)
Mean MK-422	35	-	33
Mean Total Drug	49	-	48
MK-422/Total Drug (Geometric mean)	0.70**	-	0.68**
HCTZ	-	55	52

* Average of days 7-10 for MK-422; days 6-10 for HCTZ
** significant difference, $p < .05$

Power of Detecting Differences Between Treatment A, MK-421 Alone (or B, HCTZ alone) and Treatment C (MK-421/HCTZ Combination), at the $\alpha = .05$ Significance Level for Average Steady State Urinary Recovery* is given below.

	Detectable Difference			
	10%	15%	20%	25%
MK-421	.51	.87	.99	.99+
Total Drug	.66	.95	.99+	.99+
HCTZ	.47	.83	.98	.99+

*Average of recoveries for Days 7-10 for MK-422 and total drug, and Days 6-10 for HCTZ.

III. Effect of Multiple Doses of E.M. on Single dose HCTZ

	TxB* (HCTZ-S.S.)	Tx A-day 11 (MK 421-S.S. + HCTZ-S.D.)
Mean Urinary Recovery HCTZ	55	50 (No significant difference)

The effect of multiple doses of HCTZ on a single dose of E.M. could not be assessed because urine samples were missing for day 11 of TxB.

*average of days 6-10

IV. Cmax and Tmax

A.

	Tx A - Day 4 (MK-421-S.D.)	TxB - Day 11 (MK-421-S.D.+HCTZ-S.S.)	Tx C - Day 4 (MK-421-S.D.+HCTZ-S.D.)
MK-422*			
Cpmax (ng/nl)	56.1	68.1	56.9
tmax(hrs)	4.4	3.9	4.1

S.D. + single dose; S.S. = steady state

*No significant differences for all treatments.

B.

	TxB-day 4 (HCTZ-S.D.)	TxA-day 11 (MK-421 S.S. + HCTZ S.D.)	TxC-day 4 (MK 421-S.D. + HCTZ S.D.)
HCTZ			
Cmax (ng/ml)	128.0	129.4	128.0
tmax (hrs)	2.3	2.4	2.5

Table 17-7: Individual and mean Cmax and Tmax for treatments

Table 17-8: Individual and mean steady-state urinary recoveries of MK-422, Total Drug and HCTZ for treatments

Table 17-9: Individual and mean urinary recovery of Total Drug for treatment indicated

Table 17-10: Individual and mean urinary recovery of HCTZ for treatment indicated

Table 17-11: Individual and mean Urinary recovery of HCTZ for treatment indicated.

Statistical Methods:

Parameters were analyzed for differences between treatments using ANOVA for a crossover design. Urinary recovery ratio analysis was performed on the log of the ratios.

Firm's Conclusions:

Based on urinary excretion data, concomitant multiple doses of MK-421 and HCTZ have little or no effect on the bioavailability of MK-422 and HCTZ.

GDM/dea/kek/smj/2530x (3/14/84)

NDA 18-998
Enalapril Maleate
Study #570
Wang #2513x

Merck Sharp and Dohme
Submisison Date:
January 31, 1984

Title: An Open, Randomized, Single Dose, 3-Period Crossover Study to Determine the Possible Interaction of Enalapril with Propranolol in Normal Volunteers

Investigator/Site:

Objective: To determine the effect of enalapril on plasma and urine concentrations of propranolol when co-administered in a single dose. To determine the effect of propranolol on plasma and urine concentrations of enalapril when co-administered in a single dose.

Design: Open, randomized, single dose, 3-way, balanced crossover design.

Dosing: a. Enalapril Maleate (MK-421) capsule 10 mg, PO
b. dl-propranolol (Inderal ICI) tablet 80 mg, PO
c. Enalapril 10 mg + dl-propranolol 80 mg; PO
10 day washout period between treatments; fasting conditions.

Subjects: 12 normotensive healthy adult (21-25 year old) male volunteers within ± 15% of IBW (Met. Life Insurance Statistics Bulletin, 1959) and judged healthy by laboratory screen (hematology, blood chemistry, urinalysis), PE and EKG. Exclusion Criteria: previous ingestion of captopril, history of cardiac, renal, GI or allergic disease, bradycardia (50 BPM), history of asthma or skin rashes, drug/alcohol abuse, proteinuria 150 mg/d, WBC 4000/cu.mm.

Concurrent Medications: None allowed. No other drugs 7 days prior to and until completion of study.

Specimens:
Blood - 0, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post dose.
Urine (intervals): 0-1, 1-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72 and 72-96 hours post dosing.

Analytical Methods:

1. Standard Curves- see Table 570-1 and 2 and Figure 570-1
2. Linear Range - 10-100 ng/ml; see Figure 570-1
3. Limits of Sensitivity: lower 10 ng/ml (possibly lower if necessary); upper-100 ng/ml (higher if necessary)
4. Reproducibility- Mean and SD are given in Table 570-2. Coefficients of variation were respectively 5.2 and 3% for I-propranolol and 4.3 and 5.2 for d-propranolol.

Results:

	Propranolol	Propranolol plus Enalapril Maleate	Ratio*
l-propranolol (mean) AUC (ng•hr/ml)	175.95	196.30	1.11
d-propranolol (mean) AUC (ng•hr/ml)	117.21**	125.22**	1.09

	Enalapril	Enalapril Maleate plus Propranolol	Ratio*
Mean Urinary Recoveries[a]			
MK-422	36	24	.69
Total Drug	53	36	.70
MK-422/Total Drug	0.68[b]	0.66[b]	.98

a. Expressed as % of administered MK-422 equivalents
b. Geometric Means
* ratio of single entity to propranolol and enalapril maleate
** means for those subjects with data for both treatments.

Tables:

Table 570-3: Individual and mean urinary recovery of MK-422 and Total Drug with and without administration of propranolol.

Table 570-4: Individual and mean AUC (0-infinity) for propranolol with and without administration of enalapril maleate.

Figure 570-2 and 3: Mean d and L propranolol serum profiles with and without administration of enalapril maleate.

Figure 570-4: Mean MK-422 serum profile with and without administration of propranolol.

Firm's Conclusion:

1. The bioavailability of both d- and l-propranolol appears to be increased slightly (10%) when single doses of propranolol and E.M. are co-administered.

2. The availability of MK-422 is significantly ($P < .01$) reduced (30%) when single doses of E.M. and propranolol are co-administered. This reduction in availability may be secondary to a decrease in drug absorption rather than to a decrease in the extent of hydrolysis.

GDM/dea/kek/smj/2513x (10/3/84)

NDA 18-998
Enalapril Maleate
Study #634
Wang #2515x

Merck, Sharp and Dohme
Submission Date:
January 31, 1984

Title: An Open, Randomized, Single-Dose, 3-period, Crossover Study to Determine the Possible Interaction of Enalapril with Digoxin in Normal Volunteers

Investigator/Site:

Objective: 1. To determine the effect of single doses of digoxin on serum levels and urinary excretion of enalapril, and
2. to determine the effect of single doses of enalapril on plasma levels of digoxin.

Design: Open, randomized, single-dose, three-way complete crossover

Dosing: a. Enalapril maleate 10 mg P.O. (Capsule)
b. Digoxin 0.25 mg, P.O.
c. Enalapril maleate 10 mg P.O. + Digoxin 0.25 mg P.O.
Two week washout period between treatments; breakfast allowed 2 hours after dosing

Subjects: 12 healthy, normotensive, adult (19-35 year old) male volunteers within ± 15% IBW and judged normal on the basis of medical history, P.E., laboratory screen (hematology, clinical chemistry, urinalysis). Exclusion criteria: drug allergies, history of cardiac, renal, hepatic or GI disease, regular drug use, drug/alcohol abuse.

Concurrent Medications: None allowed seven days prior to or during the study. However, subject #6 took paracetamol after regimen B.

Specimens:
Blood (E.M. alone or E.M. + digoxin) -0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72 hours post dosing. (Digoxin alone) -0, 2, 4, 8, 12, 24 hours post dosing.

Urine (E.M. only) intervals: -1 to 0, 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 hours post dose.

Analytical Methods:

Results:

Mean Urinary Recovery* of MK-422 and Total Drug (TD)

	MK-422	Total Drug	MK-422/TD
E.M. alone	27	42	0.64**
E.M. + Digoxin	27	42	0.64**

* expressed as % of administered MK-422 equivalents
** geometric mean

The relative bioavailability (MK-422 urinary recovery ratio, treatment C/A) of MK-422 from treatment C compared to treatment A is 0.96 (geometric mean of individual subject ratios)

Tables:
Table 634-1: Relative bioavailability of MK-422 from treatment C compared to treatment A

Table 634-2: Individual and mean urinary recovery of MK-422 and Total Drug with and without administration of digoxin.

Figure 634-1: Mean MK-422 urinary excretion rate plot with and without administration of digoxin

Figure 634-2: Mean MK-422 serum profile with and without administration of digoxin

Figure 634-3: Mean urinary excretion rate plot for Total Drug following administration of enalapril maleate with and without digoxin

Since a nonspecific digoxin assay was utilized, no pharmacokinetic parameters or variables were calculated.

Firms Conclusions:

1. The rate and extent of absorption and disposition of enalapril following oral administration of a single 10 mg capsule of E.M. are not influenced by concomitant administration of a single 0.25 mg digoxin tablet.

GDM/dea/kek/smj/2515x (3/14/84)

NDA 18-998
Enalapril Maleate
Study #618
Wang #2518x

Merck Sharp and Dohme
Submission Date:
January 31, 1984

Title: An Open, Randomized, Single-Dose, 3-Period, Crossover Study to Determine the Possible Interaction of Enalapril with Furosemide in Normal Volunteers

Investigator/Site: [redacted]

Objective:

a. To determine the effect of E.M. on plasma and urine levels of furosemide after coadministration

b. To determine the effect of furosemide on serum and urine levels of enalapril after coadministration

Design: Open, randomized, single-dose, 3-way, balanced, crossover design

Dosing:

a. Enalapril Maleate-10 mg, P.O. (capsule)
b. Furosemide-80 mg P.O. (2 x 40 mg tablets)
c. Enalapril maleate 10 mg and furosemide 80 mg P.O.

Two-week washout period between treatments: Drug was given approximately 2 hours before breakfast under fasting conditions.

Subjects: 12 healthy normotensive adult (19-23 year old) male volunteers within 15% of Ideal Body Weight (Metropolitan Life Insurance Company Statistical Bulletin, 40, November-December, 1959) and judged to be normal by medical history, P.E. laboratory tests (hematology, blood chemistry, urinalysis) and EKG. Exclusion criteria: drug allergies, history of cardiovascular, hepatic, renal or GI disease, history of drug-related skin-rash or leukopenia, regular drug use, history of drug/alcohol abuse.

Concurrent Medications: No other drugs taken seven days prior to or during the study.

Specimens:

Blood- 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post dosing.

Urine (Intervals): -1 to 0, 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 hours.

Analytical Procedures:

Results: Table 618-2 provides values for Tmax, Cmax, AUC and cumulative urinary excretion for furosemide. Urinary excretion data for MK-422 and 422 plus Enalapril (total drug) is given below.

72-hour Urinary Recovery of MK-422 and Total Drug *

	Enalapril Maleate (E.M.)	E.M. plus Furosemide
	Mean ± S.D.	
MK-422	39 ± 4.1	38 ± 5.1
Total Drug	57 ± 6.3	56 ± 5.1
MK-422/Total Drug	0.69 (geometric)	0.68 (geometric)

* expressed as % of MK-422 equivalents administered

Tables:

Table 618-3: Individual and mean AUC (0 to 12 hrs) for furosemide administered alone and with enalapril maleate.

Table 618-4: Individual and mean 72 hour urinary recovery of furosemide administered alone and with enalapril maleate.

Table 618-5: Individual and mean 72 hour urinary recovery of MK-422 and Total Drug following administration of enalapril maleate alone and with furosemide.

Table 618-6: Individual and mean treatment ratios for Furosemide and MK-422 urinary recovery.

Figure 618-3: Mean furosemide plasma profiles with and without administration of enalapril maleate.

Figure 618-4: Mean MK-422 serum profiles with and without administration of enalapril maleate.

Firm's Conclusion:

1. Single doses of enalapril maleate (10 mg) and furosemide (80 mg) do not affect the pharmacokinetics of the other agent (to more than 20%) when taken concurrently.

GDM/dea/kek/smj/2518x (3/14/84)

Study #512

Dr. Leary's MK-421
Metabolic Disposition
Study (#512)

Table 512-2

Table II: Metabolic Disposition - Serum

Variable	Treatment	N	Mean	Std	95% Confidence Interval	Overall ANOVA p	Multiple Comparisons A-B	A-C	B-C
Maximum serum conc. of total drug (ng/ml)	A	6	90.4	39.3	49.2, 131.6	-	-	-	-
Maximum serum conc. of L-154,628 (ng/ml)	A	6	59.4	20.3	38.1, 80.7	.001	**	-	-
	B	6	2.2	1.3	0.8, 3.6				
Maximum serum conc. of L-154,826 (ng/ml)	C	6	39.0	27.4	10.2, 67.8	-	-	-	-
Time to peak serum conc. of total drug (hr)	A	6	1.6	0.8	0.8, 2.4	<.001	**	**	**
	B	6	22.0	14.2	7.1, 36.9				
	C	6	7.0	1.1	5.9, 8.1				
Time to peak serum conc. of L-154,628/ L-154,826 (hr)	A	6	3.5	0.5	2.9, 4.1	<.001	**	**	**
	B	6	22.0	14.2	7.1, 36.9				
	C	6	7.0	1.1	5.9, 8.1				
AUC_0^∞ for L-154,628 (ng.hr/ml)	A	6	682	173	500, 864	.002	**	-	-
	B	6	199	69	127, 271				
AUC_0^∞ for L-154,826 (ng.hr/ml)	C	6	726	306	405, 1047				

A = [14C]-L-154,739
B = [14C]-L-154,628
C = [14C]-L-154,826

**Significant difference between the indicated treatments, $p < .01$.

Appendix II

Tables and Graphs

Order

#512
#6
#503
#518
#555
#110
#168
#53
#524
#27
#23
#17
#570
#634
#618

Table 1: Dissolution Data

Study #	Dosage Form/ Strength**	Formulation #	Dissolution Apparatus	Test Condition	Collection Time (min)	range/mean CV, % (n=6)
555	Capsule/2.5 mg	80-55-24	*	750 ml Water, 37°	10	
	10 mg	80-55-26	*	"	10	
					20	
	40 mg	80-55-28	*	"	10	
					20	
110	Tablet/10 mg	0421-OCT-026-B01	*	"	*	
523	Capsule/10 mg	80-55-20	*	"	15	
					30	
27	Tablet/10 mg	0421-OCT-008-B02	*	"	*	
53	Capsule/10 mg	0421-DFC-001-B07	*	"	*	
	Tablet/10 mg	0421-OCT-026-B01	*	"	*	
168	Tablet/ 5 mg	0421-OCT-025-C004	*	*	*	
	10 mg	0421-OCT-026-B010	*	*	*	
	20 mg	0421-OCT-007-D010	*	*	*	
	40 mg	0421-OCT-007-E006	*	*	*	
23	Tablet/40 mg	0421-OCT-006-E01	*	750 ml Water,37°	*	
17	Capsule/10 mg	0421-DFC-001-B03	*	*	20	
	Hydrochloro-thiazide Capsule/ 25 mg	C0421-DFC-002-B01	USP I 150 rpm	900 ml 0.1N HCl,37°	30	
		C0870A-DFC-003-B01	"	"	"	
570	Capsule/10 mg	80-55-20	*	750 ml Water,37°	15	
					30	
	Propranolol Tablet/80 mg	Inderal	USP II 50 rpm	"	30	
634	Capsule/10 mg	80-55-26	*	750 ml Water,37°	10	
					20	
	Digoxin Tablet/ .25 mg	Lanoxin	USP I 120 rpm	500 ml dil. HCl,37°	60	
618	Capsule/10 mg	80-55-37	*	750 ml Water,37°	10	
					20	
	Furosemide Tablet/40 mg	Dryptal	USP I 150 rpm	750 ml .05M Phosphate Buffer pH 6.8, 37°	15	
					30	

* Proposed method: 900 ml water at 37° using USP apparatus II (paddles) at 50 rpm with minute sampling. Specifications - at least % dissolution in minutes

** Enalapril maleate unless otherwise indicated

FIGURE 1

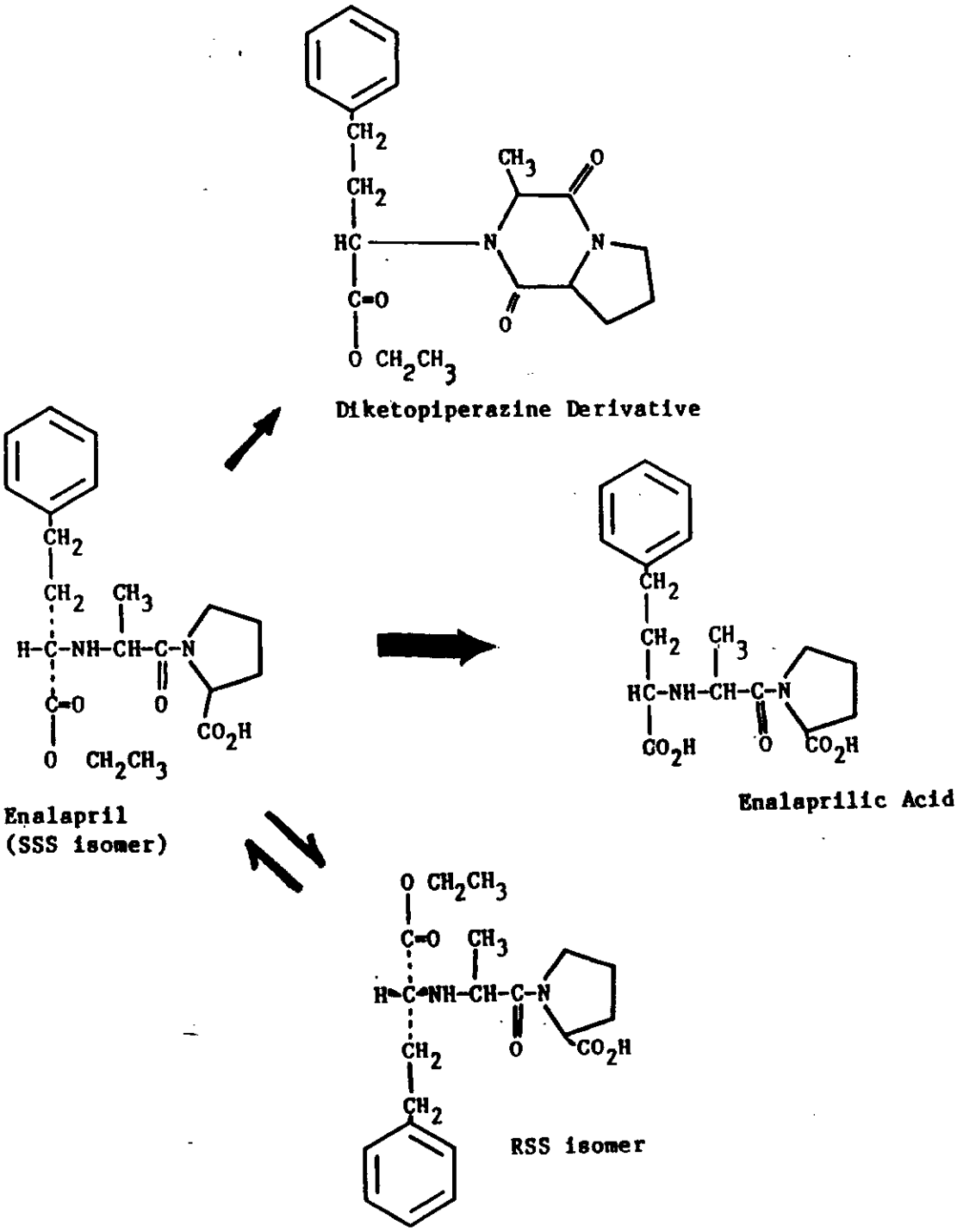
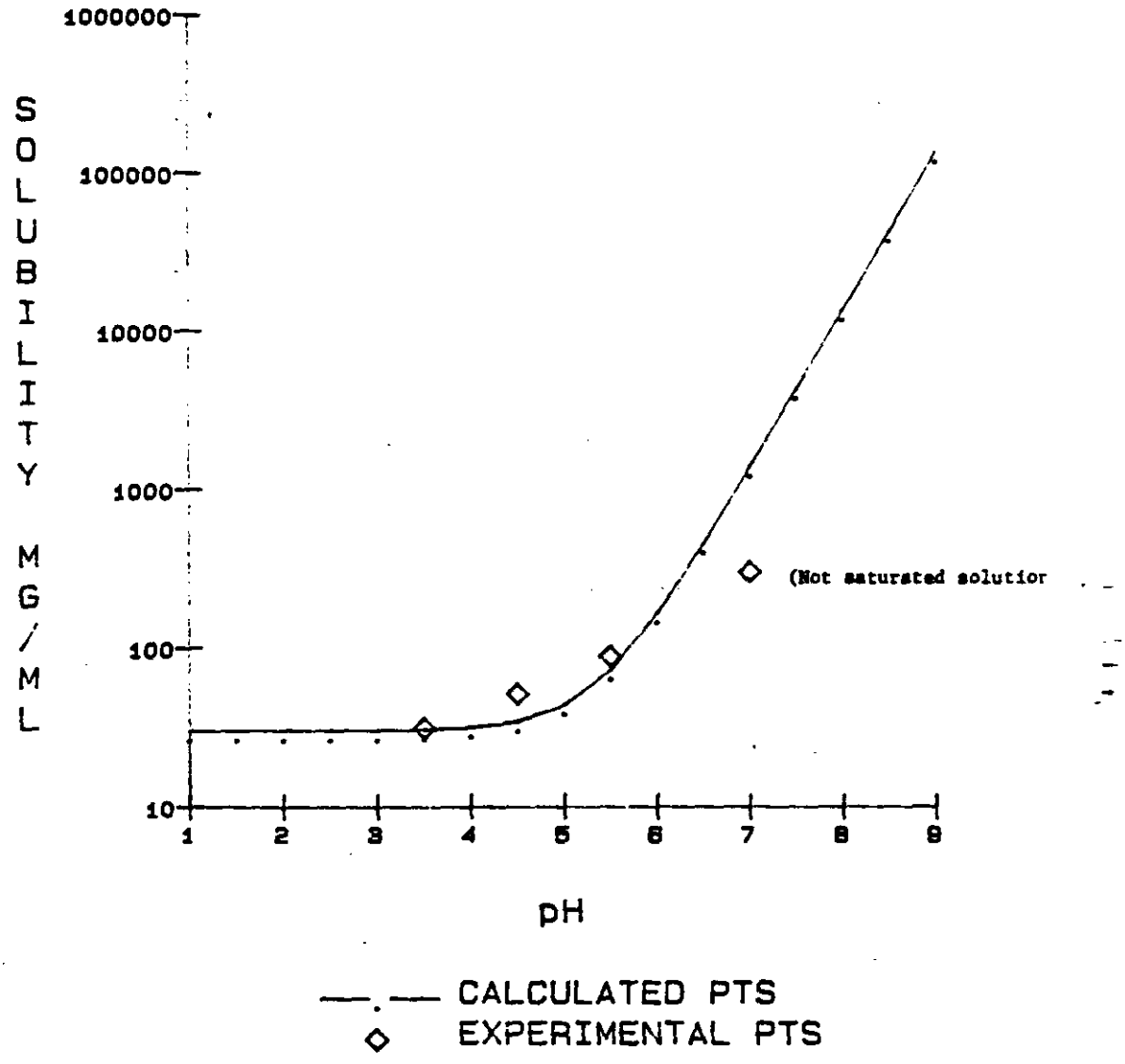

Diketopiperazine Derivative
Enalapril
(SSS isomer)
Enalaprilic Acid
RSS isomer

Figure 1a

ENALAPRIL MALEATE
pH vs SOLUBILITY PROFILE



Enalapril Maleate - pH Solubility

The pH versus solubility profile for Enalapril Maleate (attached) indicates the solubility of Enalapril Maleate increases with pH. The changes in solubility as a function of pH can be accounted for by changes in the degree of ionization of the carboxylate group on Enalapril (pKa = 5.35). Using the apparent pKa for the drug, the theoretical curve fit to the data is also shown in the figure. The less than ideal agreement between the calculated curve and experimental points is probably due to the non-ideality of the saturated solutions. The solubility of Enalapril Maleate is very high above pH 6 and is expected to change the nature of the solvent. An attempt to determine the solubility at pH 8 was discontinued when more than eight grams of material dissolved in one gram of water.

TABLE 2a Tablet Formulations* Used in Bioavailability Study #168 (10)

Ingredient	Amount per Tablet (mg) 0421-OCT-025-C004 5 mg Tablet	0421-OCT-026-B010 10 mg Tablet	0421-OCT-007-D010 20 mg Tablet	0421-OCT-007-E006 40 mg Tablet
MK-421 (Enalapril Maleate)	5.0	10.0	20.0	40.0
Sodium Bicarbonate Reagent Grade				
Lactose USP				
Starch, NF Corn				
Magnesium Stearate				
Mapico Red #347 (Iron Oxide)				
Mapico Yellow Light Lemon 100 (Iron Oxide)				

Assay: MK-421/Tab

Table 2b Enalapril Maleate Capsule and Tablet Formulations for Bioavailability Study Nos. 53, 523, and 27 (11,12,13)

Capsule			Tablet		
	Amount per DFC			Amount per C.T.	
Ingredient	80-55-20 (Study #523)	0421-DFC-001-B07 (Study #53)	Ingredient	0421-OCT-008-B02 (Study #27)	042-OCT-026-B01 (Study #53)
MK-421 (Enalapril Maleate)	10.0 mg	10.0 mg	MK-421 (Enalapril Maleate)	10.0 mg	10.0 mg
Lactose USP Hydrous Dense		mg	Sodium Bicarbonate Reagent Grade	mg	mg
Lactose Dutch, 70/100 Mesh	mg		Lactose USP 80 Mesh	mg	mg
Lactose B.P.	mg		Corn Starch NF	mg	mg
Magnesium Stearate	mg	mg	Mapico Red 347 (Iron Oxide)	mg	mg
			Magnesium Stearate NF	mg	mg
y:			Assay:		

[redacted]

Table [redacted] 2b-1

Enalapril Maleate Capsule Formulations
Used in M.A. #503, 555, 518, and 570

Ingredient	Amount/Capsule (mg)					
Study:	M.A. #503	M.A. #555			M.A. #518	M.A. #570
Enalapril Maleate	10.0	2.5	10.0	40.0	10.0	10.0
Lactose, Dutch 70/100 Mesh						
Lactose, B.P. 80 Mesh						
Magnesium Stearate						
Dissolution: (mean of 6)	--	82% min)	89% min)(	91% min)	--	98% min)

Table [redacted] 2b-2

Enalapril Maleate Tablet Formulations
Used in M.A. #23 and M.A. #110

Ingredient	Amount/Tablet (mg)	
	M.A. #23	M.A. #110
Enalapril Maleate	40.0	10.0
Sodium Bicarbonate (Reagent Grade)		
Lactose USP		
Stearate NF*		
Starch NF or Pre-Gelatinized Starch NF in Place of Starch Paste		
Purified Water USP**		
Magnesium Stearate NF		
Mapico Red 347		
Mapico Yellow 1000		
Dissolution: (n=6)	98% min)	102% min)

* Calculated on anhydrous basis
** Used to granulate; not regarded as constituent of final product

Table [redacted] 2c

Enalaprilic Acid Intravenous Formulations
Used in Bioavailability
Study Nos. 53, 523, and 27 (11,12,13)

Ingredient	L-154,628 (Enalaprilic Acid) for Injection 5 mg/ml Amount per ml 0421 HSS 001 B02 Study #53	 0421 HSS 001 B03 Study Nos. 523, 27
L-154,628	5.4 mg	5.15 mg
Sodium Phosphate Dibasic Anhydrous	mg	mg
(Added as Sodium Phosphate Dibasic 12 H_2O)		mg)
Benzyl Alcohol	mg	mg
Water for Injection	ml	ml
Assay	mg/ml	9 mg/ml

APPEARS THIS WAY
ON ORIGINAL

TABLE 2d Quantitative Composition and Dosage Form Characteristics

— Proposed Formulation —

Quantitative Compositions of Enalapril Maleate Tablets

Ingredient	Amount per Tablet (mg)			
	5 mg Tab.	10 mg Tab.	20 mg Tab.	40 mg Tab
Enalapril Maleate	5.0	10.0	20.0	40.0
Sodium Bicarbonate (Reagent Grade)				
Lactose USP				
Starch NF*				
Starch NF or Pre-gelatinized Starch NF in Place of Starch Paste				
Purified Water USP**				
Magnesium Stearate NF				
Mapico Red 347 (Red Ferric Oxide NF)				
Mapico Yellow 1000 (Yellow Ferric Oxide NF)				
Total				

* Calculated on anhydrous basis.
** Used to granulate; not regarded as constituent of final product.

Dosage Form Characteristics for Typical Lots of Enalapril Maleate Tablets

	5 mg Tablet	10 mg Tablet	20 mg Tablet	40 mg Tablet
Formulation No.	0421-OCT-025-C004	0421-OCT-026-B010	0421-OCT-007-D010	0421-OCT-007-E006
Color	White	Rust Red	Peach	Yellow
Average Assayed Tablet Drug Content (mg)	4.82	9.9	19.85	40.1
Content Uniformity				
Disintegration Time[a]				
Dissolution Time (% Tablet Drug Content)[b] - 30 min				

[a] Specification - Maximum 15 min in water at 37°C, no discs.
[b] Specification - At least Z in min.

Table 2d-1

From K.C. Kwan (MSD)
submission dated 4/9/85, NDA 18-998

This is in response to your request on April 4, 1985 to show the relationship between formulations used in bioavailability studies and those used in pivotal clinical studies of efficacy.

The formulations for the 5-, 10-, 20-, and 40-mg enalapril maleate tablets that we propose to market are given in Table 1(2d3) All four potencies have been shown to be similarly bioavailable in Study #168 . The same 5- and 10-mg formulations have been used extensively in pivotal studies of hypertension and congestive heart failure.

The 5-mg tablet formulation was used in the Multiclinic Dose Response Study in Congestive Heart Failure (#72, #58, #55, #56, #59, #57, #521, #533, #568, #567, and #591) and in the Multiclinic Placebo-Controlled Study in Patients with Chronic Congestive Heart Failure (#95, #97, #98, #101, #99, #100, #106, #102, #103, #104, and #105).

The 10-mg tablet was used in the Multiclinic Comparison with Hydrochlorothiazide and Enalapril Maleate/Hydrochlorothiazide in Mild to Moderate Hypertension (#29, #30, #31, #32, #34, #33, #35, #36, #37, #38, #39, #28, #40, #41, #42, #43, #44, #45, #46, #47, #48, #49, #50 and #51).

Capsule formulations (2.5, 10, 20 and 40 mg) were used in the Multiclinic Dose Response in Hypertension Study (#61, #62, #63, #64 and #65). Bioequivalence of the 10-mg capsule formulation to the 10-mg market formulation tablet was documented in bioavailability Study #53 .

The overseas Multiclinic Placebo-Controlled Study in Patients with Congestive Heart Failure (#598, #621, #674, #557 and #574) used in support of a congestive heart failure claim used a 5-mg enalapril maleate tablet which differed only slightly from the market formulation, i.e., 22.0 mg corn starch vs. 25.3 mg, 168.5 mg lactose vs. 196.0 mg, and 1.0 mg magnesium stearate vs. 1.15 mg. These differences are insignficant in light of the demonstrated bioequivalence among formulations in the study (#168).

Finally, for your convenience, the locations of the above-cited studes in the NDA are shown in Table 2.(2d-2)

Table 2d-2

Table 2

Location of Pivotal Clinical Studies and Key Bioavailability [illegible] Studies in New Drug Application 18-998 - Enalapril Maleate

Study	Volume No.	Starting Page
Multiclinic Dose Response in Hypertension (#61, #62, #63, #64, #65)	3.19	I-07152
Multiclinic Dose Response in Congestive Heart Failure (#72, #58, #55, #56, #59, #57, #521, #533, #568, #567, #591)	3.22	I-08453
Multiclinic Comparison with Hydrochlorothiazide and Enalapril Maleate/Hydrochlorothiazide in Mild to Moderate Hypertension (#29, #30, #31, #32, #34, #33, #35, #36, #37, #38, #39, #28, #40, #41, #42, #43, #44, #45, #46, #47, #48, #49, #50, #51)	3.24	I-09314
Multiclinic Placebo-Controlled Study in Patients with Chronic Congestive Heart Failure (#95, #97, #98, #101, #99, #100, #106, #102, #103, #104, #105)	3.11 and 3.12	IA-25423 -25499 -26073 -25550 -25616 -25706 -25735 -25860 -25943 -25984 -26009
Multiclinic Placebo-Controlled Study in Patients with Congestive Heart Failure (#598, #621, #674, #557, #574)	3.113	IA-26195 -26304 -26354 -26420 -26440
Bioavailability of Final Market Image Tablets (#168)	3.333	VII-00018
Capsule and Tablet Bioavailability (#53)	3.333	VII-00019

Table 2d-3

Table 1

Market Formulations of Enalapril Maleate Tablets

Ingredient	Amount per Tablet (mg)			
	5 mg Tab.	10 mg Tab.	20 mg Tab.	40 mg Tab
Enalapril Maleate	5.0	10.0	20.0	40.0
Sodium Bicarbonate (Reagent Grade)				
Lactose USP				
Starch NF*				
Starch NF or Pre-gelatinized Starch NF in Place of Starch Paste				
Purified Water USP**				
Magnesium Stearate NF				
Mapico Red 347 (Red Ferric Oxide NF)				
Mapico Yellow 1000 (Yellow Ferric Oxide NF)				
Total				

* Calculated on anhydrous basis.
** Used to granulate; not regarded as constituent of final product.

Table 2e

Pivotal Study Data Summary (Mean Parameters)

Study No.	Dosage Form/Route	Dose (mg)	Enalaprilic Acid C_{max} (ng/ml)	Enalaprilic Acid T_{max} (h)	$t_{1/2}$ (h)	Urinary Recovery: Enalaprilic Acid[a] (% Dose)	Urinary Recovery: Total Drug[b] (% Dose)	Urinary Recovery: Enalaprilic Acid/Total Drug[c]
6	Enalaprilic Acid/ i.v.	2.5	—	—	—	92	—	—
		5	—	—	—	96	—	—
		10	—	—	—	93	—	—
518	Capsule/p.o.	10 mg q24hx8			11.1[d]	45[e]	62[e]	.71[e]
555	Capsule/p.o.	2.5	5.9	6	—	28	46	.58
		10	32.3	4	—	33	52	.62
		40	149.8	3	—	36	53	.65
	Enalaprilic Acid/ i.v.	5	—	—	—	92	—	—
53	Capsule/p.o.	10	37.5	3.6	—	42	61	.68
	Tablet/p.o.	10	45.1	3.8	—	40	63	.65
	Enalaprilic acid/ i.v.	5	—	—	—	106*	—	—
168	Tablet/p.o.	5	15.3	4.8		35	56	.63
		10	37.4	3.9		41	65	.64
		20	70.8	3.2		36	56	.65
		40	123.1	3.4		34	53	.64
	Enalapril Maleate/ i.v.	5	16.5	4.0		39	86	.45
	Enalaprilic Acid/ i.v.	5	—	—		90	—	—

[a] Estimate of bioavailability.
[b] Estimate of minimum absorption; total drug equals enalaprilic acid measured after sample hydrolysis and represents enalaprilic acid plus enalapril which was present in the sample.
[c] Approximation of extent of hydrolysis; geometric mean of individual values.
[d] Effective half-life for accumulation.
[e] Cumulative recovery for 8 doses.
* Greater than 50% of subjects had values of more than 100% indicating actual dose administered is underestimated by nominal dose.

TABLE 3

A Sample Standard Curve* for the
of Enalaprilic Acid

Nominal Concentration (ng/ml)	Read-back Concentration (ng/ml)	%B/B_o
		90.7
		82.2
		72.8
		60.2
		41.2
		28.3
		18.5
		10.4
		7.47

% bound, 39.0
% NSB, 0.96
Conc. for 50% inhibition, 6.48 ng/ml

* Book 7853 p.251 (file XL)

TABLE 4

Quality Control Data* for

	Nominal Concentration	Assayed Concentration	Inter-assay CV (%)	Intra-assay CV (%)	(N)
Serum[a]:					
Enalaprilic Acid	ng/ml	ng/ml	5.0	6.8	(15)
			3.8	4.8	(15)
			5.5	7.6	(13)
Enalapril Maleate**	ng/ml	ng/ml	6.3	8.4	(43)
			3.8	7.5	(43)
			4.7	7.9	(41)
Urine[b]:					
Enalaprilic Acid	µg/ml	µg/ml	5.7	7.2	(68)
			3.9	6.5	(68)
			5.5	5.9	(67)
Enalapril Maleate**	µg/ml	µg/ml	6.6	10.9	(46)
			4.1	9.2	(46)
			4.9	9.9	(46)

* Current as of June 1983
** Expressed in terms of enalaprilic acid
a Book 7853-229 (file XL)
b Book 7912-81 (file XXXVIII)

TABLE 5

Analytical Methods Summary

Study No.	Biological Fluid	Assay Method	Lower Limit For Assay Validity	Moieties Analyzed
512	Serum			Total ^{14}C
				Enalaprilic acid*
	Urine			Total ^{14}C
				Enalaprilic acid
				Enalapril
				Enalaprilic acid*
	Feces			Total ^{14}C
503	Serum			Enalaprilic acid*
				Enalaprilic acid*
	Urine			Enalaprilic acid*
	Feces			Enalaprilic acid*
518	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*
6	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*
555	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*

* Enalaprilic acid is measured both before and after hydrolysis, enabling determination of enalaprilic acid itself and total drug (enalaprilic acid plus enalapril).
** Selected samples.

(con't)

Study No.	Biological Fluid	Assay Method	Lower Limit For Assay Validity	Moieties Analyzed
110	Serum			Enalaprilic acid*
	Plasma**			Enalaprilic acid*
	Urine			Enalaprilic acid*
523	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*
27	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*
53	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*
168	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*
23	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*
17	Serum			Enalaprilic acid*
				Hydrochlorothiazide
	Urine			Enalaprilic acid*
				Hydrochlorothiazide

* Enalaprilic acid is measured both before and after sample hydrolysis, enabling determination of enalaprilic acid itself and total drug (enalaprilic acid plus enalapril).
** For subjects on hemodialysis.
*** Lowest concentration on standard curve.

TABLE 5 (con't)

Analytical Methods Summary

Study No.	Biological Fluid	Assay Method	Lower Limit For Assay Validity	Moieties Analyzed
570	Serum			Enalaprilic acid* Propranolol (d- and l-)
	Urine			Enalaprilic acid*
634	Serum			Enalaprilic acid*
	Urine			Enalaprilic acid*
618	Serum			Enalaprilic acid*
	Plasma			Furosemide
	Urine			Enalaprilic acid* Furosemide***

* Enalaprilic acid is measured both before and after sample hydrolysis, enabling determination of enalaplic acid itself and total drug (enalaprilic acid plus enalapril).

** Lowest concentration on standard curve.

*** Measured before and after hydrolysis of the glucuronide.

TABLE 6

[redacted]

Tablets

TRADEMARK

(Enalapril Maleate, MSD)

HOW SUPPLIED

No. 3412 - Tablets Trademark, 5 mg, are white barrel shaped, compressed tablets, with code MSD 712 on one side and Trademark on the other. They are supplied as follows:

NDC 0006-0712-68 bottles of 100 (with desiccant)

NDC 0006-0712-28 single unit packages of 100

NDC 0006-0712-58 unit of use bottles of 100 (with desiccant).

No. 3413 - Tablets Trademark, 10 mg, are red, barrel shaped, compressed tablets, with code MSD 713 on one side and Trademark on the other. They are supplied as follows:

NDC 0006-0713-68 bottles of 100 (with desiccant)

NDC 0006-0713-28 single unit packages of 100

NDC 0006-0713-58 unit of use bottles of 100 (with desiccant).

No. 3414 - Tablets Trademark, 20 mg, are peach, barrel shaped, compressed tablets, with code MSD 714 on one side and Trademark on the other. They are supplied as follows:

NDC 0006-0714-68 bottles of 100 (with desiccant)

NDC 0006-0714-28 single unit packages of 100

NDC 0006-0714-58 unit of use bottles of 100 (with desiccant).

No. 3415 - Tablets TRADEMARK, 40 mg, are yellow barrel shaped, compressed tablets, with code MSD 715 on one side and TRADEMARK on the other. They are supplied as follows:

NDC 0006-0715-68 bottles of 100 (with desiccant)

NDC 0006-0715-28 single unit packages of 100

NDC 0006-0715-58 unit of use bottles of 100 (with desiccant).

Table 7

[redacted] · Effect of captopril infusion on serum concentration (ng/ml) profile of intravenous MK-422 in dogs. *

Dog # (body wt)	①Dose MK-422 mg/kg	②Captopril Infusion (dose) mg/kg/day	Time after MK-422 Hours 0.5	1.0	2.0	4.0	6.0	24	30	48	54	72	78
80-0588	0.21	-----											
80-0588(11.4kg)		12.8											
41921	0.21	-----											
41921(12.2kg)		10.0											
084085	0.10	-----											
084085(8.2kg)		17.6											
520270	0.10	-----											
520270(8.0kg)		10.0											
65099	0.05	-----											
65099(8.0kg)		20.0											
65374	0.05	-----											
65374(9.2kg)		19.2											

Underlined values are apparent outliers.
MK-421 XIV
7277/341,343
7277/369

①[redacted] Metab III
7339-131, 132, 145
②[redacted] Metab III
7339-145, 146

? * - Displayed graphically in Figs 3 and 4

[redacted]

Table 8 *

[redacted] Mean serum concentrations (ng/ml) of MK-422 in dogs (n=5) receiving MK-422 i.v. plus or minus captopril infusion. (Dogs)

	Hours	0.5	1.0	2.0	4.0	6.0	8.0	12	18	24	30	48	54	72
MK-422	X													
	±SD													
30-72 hr extrapolation														
Δ (MK-422 - extrapolation)														
MK-422 with captopril infusion	X	263	136	51.6	15.3	7.0	3.4	1.1	0.4	0.1	0	0	0	
	±SD	26.1	18.8	6.7	1.8	1.2	0.3	0.2	0.1	0.1				

Notebook/Page
MK-421 File XIX
7594/207-209
7594/215-216
7594/219-222

* - Displayed graphically in Fig [redacted] 2

Figure 2

[redacted] Serum concentration profile of MK-422 i.v. with and without continuous captopril infusion. (Dogs)

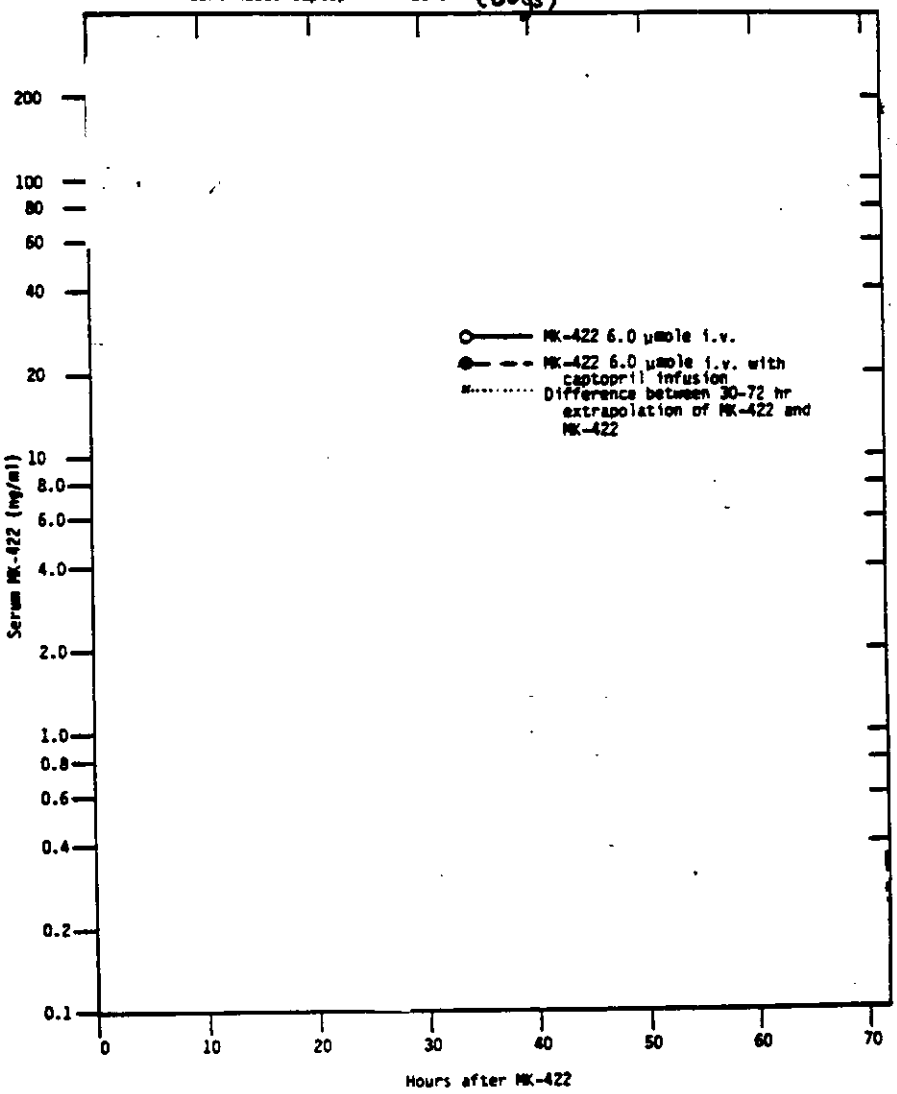


Table 9

[redacted] Dose of MK-422 administered. (Dogs)

Dose regimen for data in Table 8 [redacted] and fig 2.

Dog #	Wt(kg)	Dose MK-422 (6 µmole)	Period I	Period II
142875	11.0	0.19 mg/kg	(+)	(-)
146064	9.5	0.22 mg/kg	(-)	(+)
148644	10.5	0.20 mg/kg	(+)	(-)
148903	10.2	0.21 mg/kg	(-)	(+)
149560	11.0	0.19 mg/kg	(-)	(+)
35041	12.5	0.17 mg/kg	(-)	(+)

(-) - MK-422 alone
(+) - MK-422with captopril

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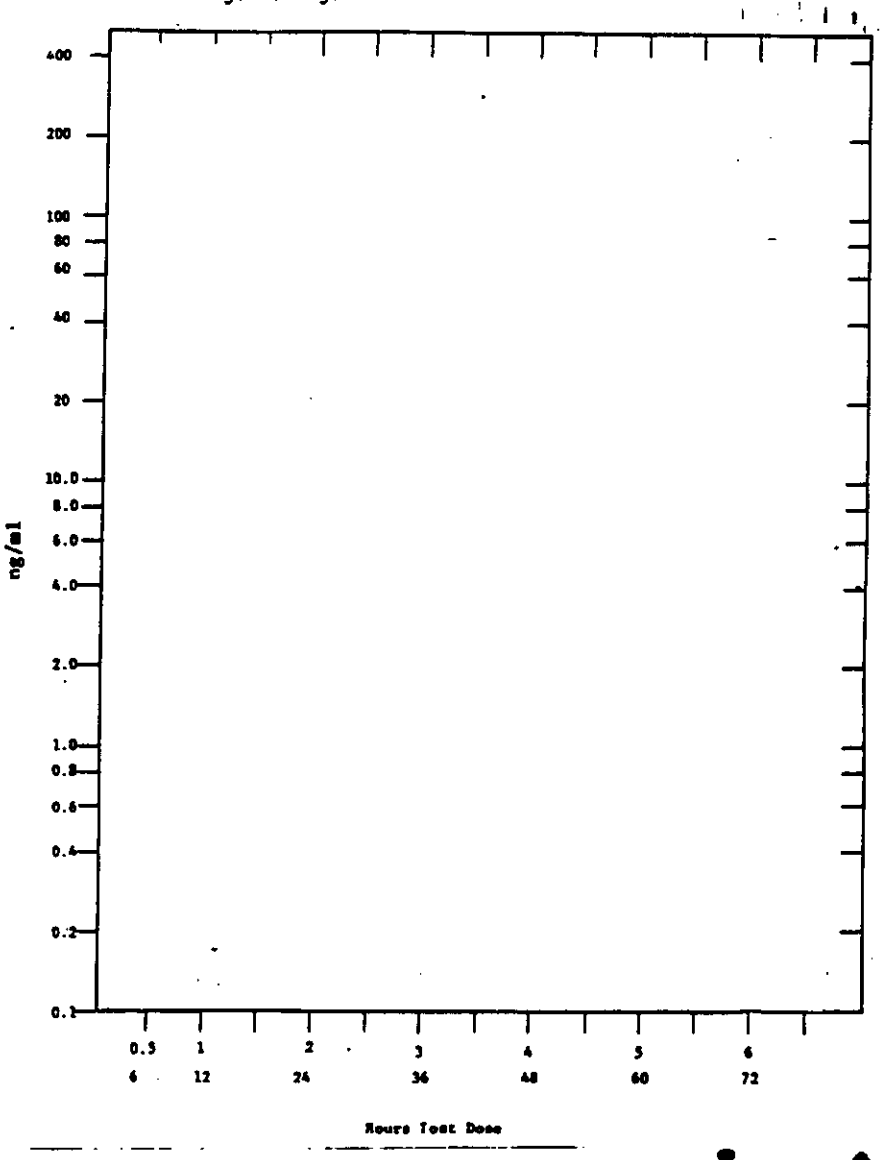
Figure 3

[redacted] Serum concentration profiles of MK-422 after i.v. dosage to dogs

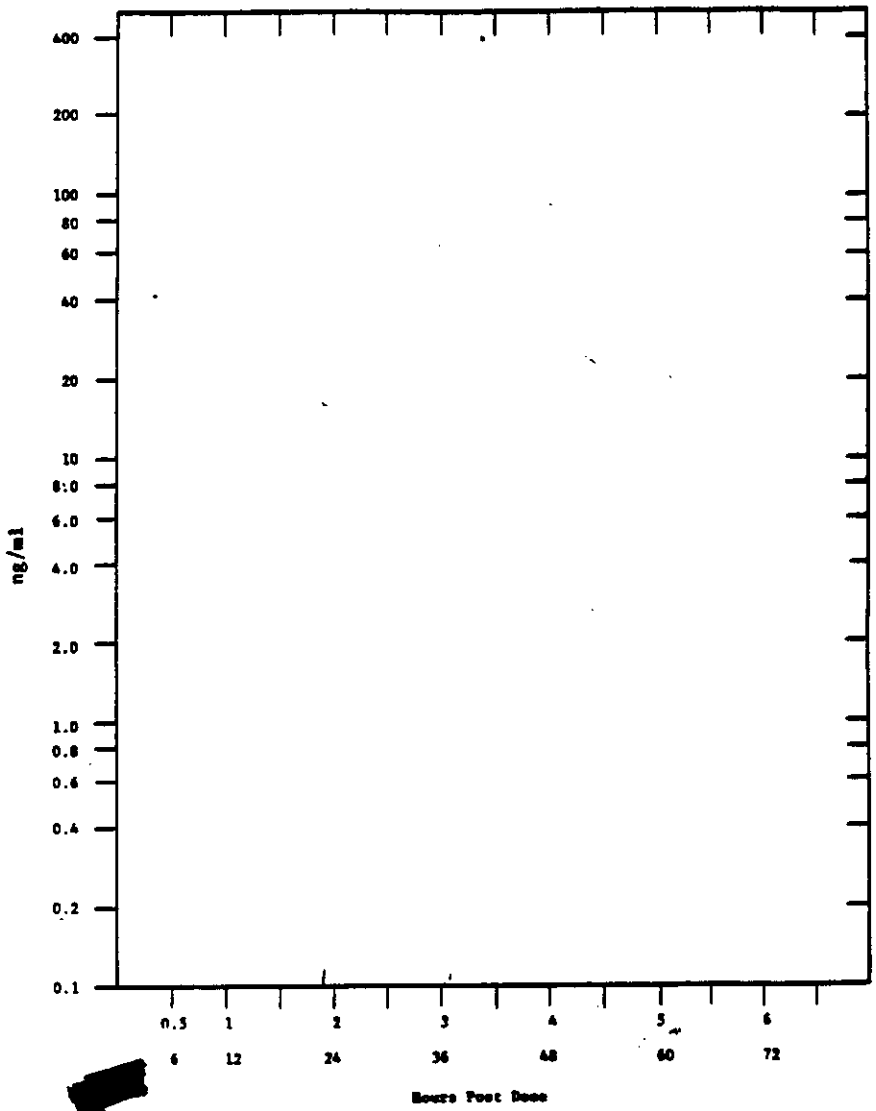


One of three doses of MK-422 was administered to dogs. (0.21 mg/kg; 0.10 mg/kg and 0.05 mg/kg). Two time scales are used. The upper scale refers to the higher concentrations observed over the initial 6 hrs and the lower scale refers to the terminal phase.

Points with * are from one animal; all others are the average from 2 animals.

Figure 4

[redacted]. Serum concentration profiles of MK-422 after i.v. dosage to dogs with continuous infusion of captopril. (Dogs)



[redacted]

One of three doses of MK-422 was administered to dogs receiving a continuous infusion of captopril for 6 hrs prior to dosage with MK-422 i.v. and for the remainder of the experiment. Two time scales are used. The upper scale refers to the higher concentrations observed in the initial 6 hrs and the lower scale refers to the terminal phase. MK-422 doses were 0.21 mg/kg (●), 0.10 mg/kg (▲), and 0.05 mg/kg (■).

« 10

[redacted]. Binding of enalaprilat to pooled human plasma determined by ultrafiltration.

[Free][a]	[Bound][b]	Total	B/F[c]	%B
0.67 nM	2.3 nM	2.97 nM	3.5	78
0.70	2.3	3.0	3.3	77
0.66	2.3	2.96	3.6	78
3.6	6.4	10	1.8	64
4.0	6.0	10	1.5	60
3.7	6.3	10	1.7	63
13	17	30	1.2	55
15	15	30	1.0	50
14	16	30	1.1	53
46	54	100	1.2	54
54	46	100	0.87	46
51	49	100	0.98	49
170	130	300	0.79	44
150	150	300	1.0	51
170	130	300	0.75	43
590	410	1000	0.69	41
600	400	1000	0.66	40
580	420	1000	0.73	42

Linear regression of B/F vs B for the two lowest concentrations yielded:
Kd = 2.2 nM[c]
Capacity = 10 nM[c]

Linear regression of B/F vs B for the three highest concentrations yielded:
Kd = 1.5 μM[c]
Capacity = 1.5 μM[c]

[a] Concentrations were determined directly on ultrafiltrates using DM-019 (enzyme inhibition).

[b] Calculation on basis of total concentration added to sample and free concentration.

[c] Determined using unrounded numbers and therefore may vary slightly from values calculated using values in table.

Table 11

[redacted]. Binding of enalaprilat to pooled human plasma determined by equilibrium dialysis.

[Free][a]	[Bound][b]	Total	B/F[c]	%B
1.3 nM	3.4 nM	4.7	2.6	72
1.4	3.1	4.6	2.2	68
5.9	8.3	14.2	1.4	59
5.9	8.1	14	1.4	58
21	17	38	0.82	45
20	20	40	1.0	50
22	17	39	0.78	44
76	48	124	0.64	39
79	43	122	0.55	35
260	88	348	0.34	26
230	130	360	0.58	37
880	240	1120	0.28	22
880	240	1120	0.28	22

Linear regression of B/F vs B for the two lowest concentrations yielded:
Kd = 5.1 nM[c]
Capacity = 15 nM[c]

Linear regression of B/F vs B for the three highest concentrations yielded:
Kd = 0.72 μM[c]
Capacity = 0.46 μM[c]

[a] Concentrations were determined directly on dialysates using DM-019 (enzyme inhibition).

[b] Calculation on basis of total concentration added to sample and free concentration.

[c] Determined using unrounded numbers and therefore may vary slightly from values calculated using values in table.

Figure 5

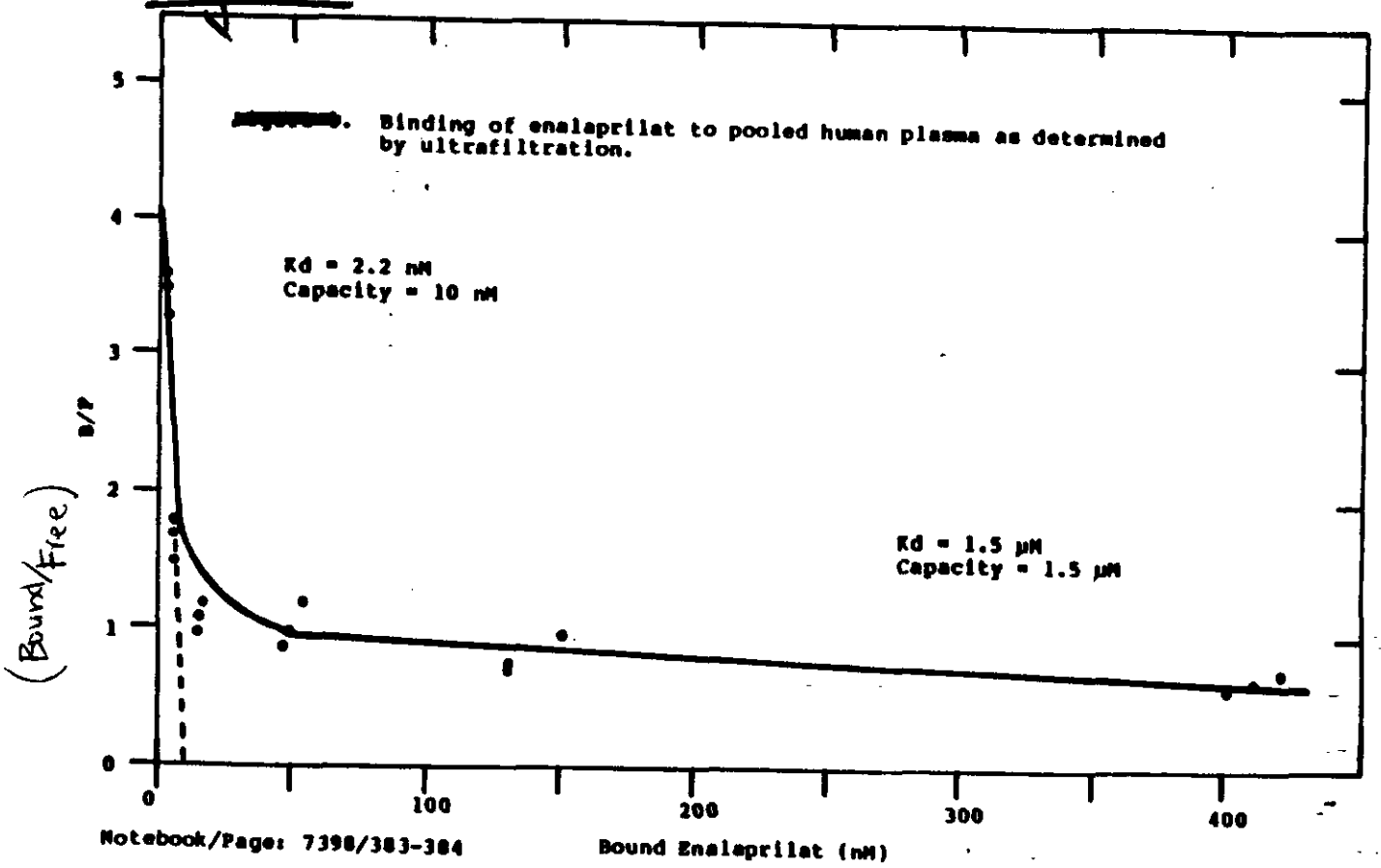
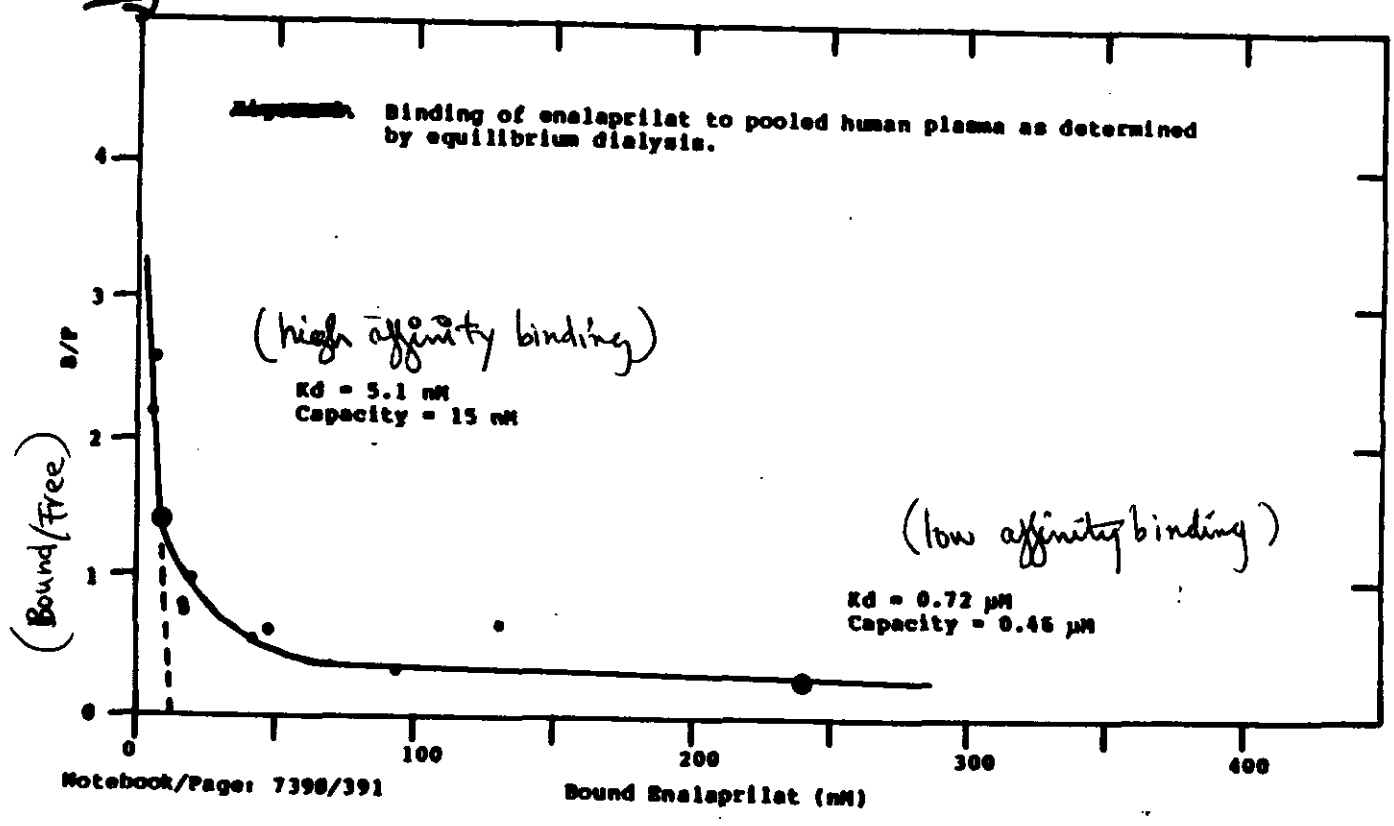


Figure 6



study #512

[redacted]

Table 512-3

[redacted]

[redacted] Material balance: μCi of ^{14}C-MK-421 excreted in urine and feces (dose = 10.968 μCi).

[redacted] (Drug ^{14}C-MK-421)

	Subject - Period						
	1-1	2-2	3-3	4-3	5-2	6-1	Mean ± S.D.
Urine							
0-2 hr							1.25 ± 0.69
2-4							1.49 ± 0.47
4-6							0.90 ± 0.32
6-8							0.72 ± 0.16
8-10							0.52 ± 0.14
10-24							0.81 ± 0.36
day 2							0.33 ± 0.14
3							0.07 ± 0.02
4							0.04 ± 0.02
5							0.02 ± 0.01
6							0.02 ± 0.01
7							0.02 ± 0.01
Total							6.17 ± 0.94
% of dose							56.2 ± 8.49
Feces							
day 1							
2							
3							
4							
5							
6							
7							
Total							2.95 ± 1.21
% of dose							26.9 ± 11.04
Urine + Feces							9.12 ± 0.89
% of dose							83.1 ± 8.10

n.s. = no sample

study # 512

MK-421
Bioavailability Study
M.A. #512; D.M. #336

[redacted]

Table # 512-4

[redacted]. Material balance: μCi of ^{14}C-L-154,628 excreted in urine and feces (dose = 10.35 μCi).

(Drug-^{14}C-L-154,628)=(MK-422)

	Subject - Period						
	1-3	2-1	3-2	4-1	5-3	6-2	Mean ± S.D.
Urine							
0-2							0.04 ± 0.02
2-4							0.04 ± 0.02
4-6							0.08 ± 0.15
6-8							0.01 ± 0.00
8-10							0.01 ± 0.01
10-12							0.07 ± 0.07
day 2							0.09 ± 0.04
3							0.05 ± 0.03
4							0.04 ± 0.02
5							0.03 ± 0.02
6							0.02 ± 0.01
7							0.02 ± 0.01
Total							0.48 ± 0.27
% of dose							4.7 ± 2.6
Feces							
day 1							5.5 ± 3.85
2							1.3 ± 0.63
3							0.2 ± 0.20
4							1.1 ± 2.67
5							0.1 ± 0.18
6							0.1 ± 0.20
7							0.01 ± 0.01
Total							8.36 ± 2.21
% of dose							80.8 ± 21.14
Urine + Feces							8.84 ± 2.25
% of dose							85.4 ± 21.74

n.s. = no sample

study # 512

Table 512-5

Concentration (ng/ml) of L-154,628 in serum of human subjects dosed with ^{14}C-MK-421.

Subject	Period	Assay[a]	Hours After Dose																
			0.0	0.5	1	1.5	2	3	4	6	8	10	14	24	48	72	96	120	144
1	1	Free																	
		Total																	
		^{14}C																	
2	2	Free																	
		Total																	
		^{14}C																	
3	3	Free																	
		Total																	
		^{14}C																	
4	3	Free																	
		Total																	
		^{14}C																	
5	2	Free																	
		Total																	
		^{14}C																	
6	1	Free																	
		Total																	
		^{14}C																	

[a]Free drug is the concentration of L-154,628 before hydrolysis
Total drug is the concentration of L-154,628 after hydrolysis
^{14}C is the ng-equivalents of L-154,628 calculated from the specific activity, 1.279 μCi/mg.

n.s. = no sample

Table # 512-6

Concentration (μg/ml) of L-154,628 in urine of human subjects dosed with ^{14}C-MK-421.

Subject	Period	Assay[a]	0-2	2-4	4-6	6-8	8-10	10-24	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	1	Free												
		Total												
		^{14}C												
2	2	Free												
		Total												
		^{14}C												
3	3	Free												
		Total												
		^{14}C												
4	3	Free												
		Total												
		^{14}C												
5	2	Free												
		Total												
		^{14}C												
6	1	Free												
		Total												
		^{14}C												

[a]Free drug is the concentration (μg/ml) of L-154,628 before hydrolysis.
Total drug is the concentration after hydrolysis.
^{14}C is the concentration in L-154,628 equivalents calculated from the specific activity, 1.279 μCi/mg.

study #512

Table #512-7 Observed Maximum Serum Concentrations (C_{max}) of Total Drug* and L-154,628 Following ^{14}C-L-154,739 Administration, and of L-154,628 Following L-154,628 Administration, and Times (T_{max}) at Which They Were Observed

	^{14}C-L-154,739				^{14}C-L-154,628	
	Total Drug		L-154,628		L-154,628	
Subject	C_{max} (ng/ml)	T_{max} (hr)	C_{max} (ng/ml)	T_{max} (hr)	C_{max} (ng/ml)	T_{max} (hr)
1						
2						
3						
4						
5						
6						
Mean	90.4	1.6	59.4	3.5	2.2	22

* L-154,628 plus "L-154,739"

Table #512-8

AUC_0^∞ (ng·hr/ml) for L-154,628 Following Oral Administration of ^{14}C-L-154,628 and ^{14}C-L-154,739

		AUC_0^∞	
Subject	^{14}C-L-154,628		^{14}C-L-154,739
1			
2			
3			
4			
5			
6			
Mean	199		682

study #512

MK-421
Bioavailability Study
M.A. #512; D.M. #336

Table 512-9

Thin layer chromatography of 0-24 hr urine from subject(a) dosed with ^{14}C-MK-421.

	Rf values (%) in solvent systems (b)			
	I	II	III	IV
Urine	0.65 (38) 0.59 (59) 0.49 (2) 0.43 (1)	0.70 (4) 0.64 (39) 0.57 (53) 0.47 (3) 0.41 (1)	0.59 (43) 0.47 (57)	0.37 (40) 0.23 (60)
MK-421	0.67	0.65	0.56	0.37
L-154,628	0.59	0.56	0.45	0.21

(a) Subject No. 2 (period 2).
(b) See Methods

Table 512-10

Urinary and Fecal Recoveries* of Radioactivity Following Oral Administration of ^{14}C-L-154,628, ^{14}C-L-154,739 and ^{14}C-L-154,826

	^{14}C-L-154,628		^{14}C-L-154,739		^{14}C-L-154,826	
Subject	Urine	Feces	Urine	Feces	Urine	Feces
1						
2						
3						
4						
5						
6						
Mean	4.6	80.7	56.1	26.9	27.9	55.9

* Expressed as percent of administered radioactivity, based on DM dosage form assay values (see Table 2).

1A

Individual AUC Values for MK-422 (ng.hr/ml) Following I.V. Doses of 2.5 mg MK-422 in 12 Healthy Volunteers

Subject	AUC_0^∞	AUC^E	$AUC_0^\infty - AUC^E$	$\frac{AUC^E}{AUC_0^\infty} \times 100\%$
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	379	105	274	27*
S.D.±	49	28	40	

E AUC for extrapolated portion.
* Geometric Mean.

1B

Individual AUC Values for MK-422 (ng.hr/ml) Following I.V. Doses of 5 mg MK-422 in 12 Healthy Volunteers

Subject	AUC_0^∞	AUC^E	$AUC_0^\infty - AUC^E$	$\frac{AUC^E}{AUC_0^\infty} \times 100\%$
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	639	100	538	15*
S.D.±	93	24	80	

E AUC for extrapolated portion.
* Geometric Mean.

1C

Individual AUC Values for MK-422 (ng.hr/ml) Following I.V. Doses of 10 mg MK-422 in 12 Healthy Volunteers

Subject	AUC_0^∞	AUC^E	$AUC_0^\infty - AUC^E$	$\frac{AUC^E}{AUC_0^\infty} \times 100\%$
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	1202	120	1082	10*
S.D.±	193	23	181	

E AUC for extrapolated portion.
* Geometric Mean

Study #6
Table 61 A, B, C

Study #6

Individual Urinary Recoveries of MK-422 (% of Administered Dose)
Following I.V. Doses of 2.5, 5 and 10 mg of MK-422
in 12 Healthy Volunteers

TABLE # 6-2

Subject	2.5 mg	5.0 mg	10.0 mg
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	92	96	93
S.D.±	10	7	9

* Incomplete urine collection.
** Missing data.

Table #6-3

Individual Renal Clearances for MK-422 (ml/min)
Following I.V. Doses of 2.5, 5 and 10 mg of MK-422
in 12 Healthy Volunteers

Subject	2.5 mg	5.0 mg	10.0 mg
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	137	155	152
S.D.±	28	30	28

Study #6

Table #6-4

Mean Serum Concentrations of MK-422 (L-154,628) (ng/ml) Following I.V. Doses of 2.5, 5 and 10 mg MK-422 in 12 Healthy Volunteers

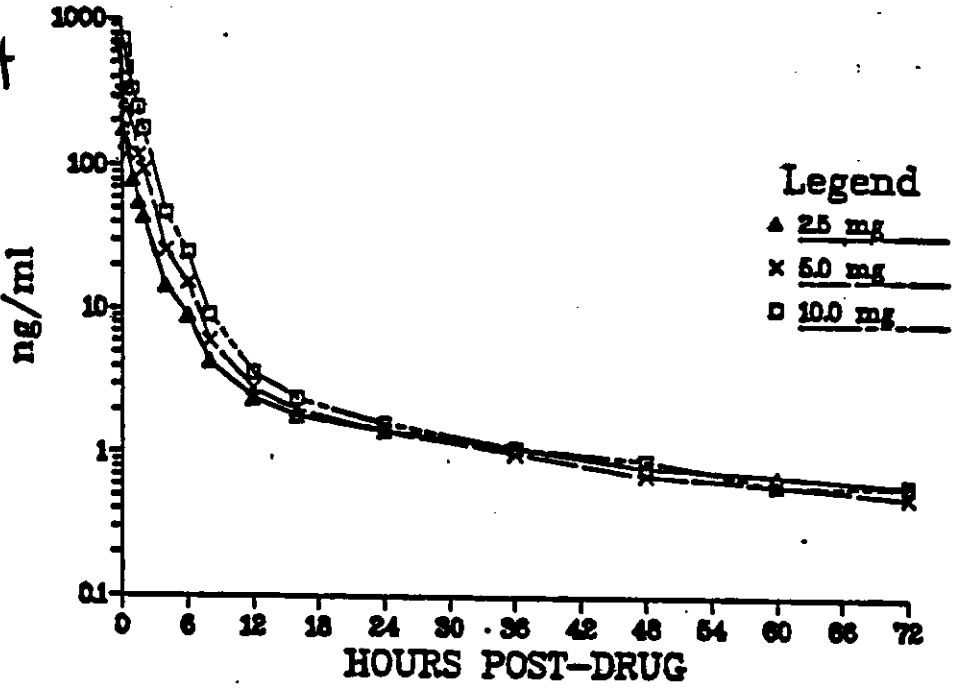


Table 6-5

Individual Slopes of MK-422 Serum Profiles (hr^{-1}) Following I.V. Doses of 2.5, 5 and 10 mg of MK-422 in 12 Healthy Volunteers

Observed Terminal Slopes*,** of L-154,628 Serum Profiles Following Intravenous Administration

Subject	2.5 mg	5.0 mg	10.0 mg
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	0.0189	0.0195	0.0192
S.D.±	0.0036	0.0034	0.0041

* hr^{-1}

** Determined by linear regression of last 3 or 4 data points.

Study #6

MK-421
M.A. #6; D.M. #345

Table 6-6

MK421 STUDY #6, DM#345 [redacted]

SERUM CONC. L-154,628, NG/ML.

SUBJ	PER	DOSE	TIME POST-DOSE															
			0	10'	20'	30'	60'	1.5H	2H	4H	6H	8H	12H	16H	24H	36H	48H	60H	72H
1	2	0																
2	4	0																
3	3	0																
4	1	0																
5	4	0																
6	3	0																
7	1	0																
8	2	0																
9	3	0																
10	3	0																
11	2	0																
12	4	0																
1	1	2.5																
2	1	2.5																
3	1	2.5																
4	2	2.5																
5	1	2.5																
6	1	2.5																
7	2	2.5																
8	1	2.5																
9	2	2.5																
10	1	2.5																
11	1	2.5																
12	1	2.5																
MEAN =			174.6	142.2	115.8	78.9	54.7	43.6	14.4	8.9	4.3	2.4	1.8	1.4	1.1	0.8	0.7	0.6
S.D. =			30.99	16.63	14.63	12.94	11.86	10.01	4.07	2.61	1.49	0.37	0.30	0.33	0.22	0.19	0.35	0.16

Table 6 (cont.)

Study #6

MK-421
M.A. #6; D.M. #345

MK421 STUDY #6, DM#345 [redacted]

SERUM CONC. L-154,628, NG/ML.

SUBJ	PER	DOSE	TIME POST-DOSE															
			0	10'	20'	30'	60'	1.5H	2H	4H	6H	8H	12H	16H	24H	36H	48H	60H	72H
1	3	5																
2	2	5																
3	2	5																
4	3	5																
5	2	5																
6	2	5																
7	3	5																
8	3	5																
9	1	5																
10	2	5																
11	3	5																
12	2	5																
MEAN =			309.7	270.5	233.9	170.3	117.0	92.5	25.5	15.1	6.0	2.8	2.0	1.4	1.0	0.7	0.6	0.5
S.D. =			68.69	47.66	32.68	23.40	24.74	20.14	7.84	6.25	3.31	0.82	0.58	0.42	0.26	0.18	0.17	0.12
1	4	10																
2	3	10																
3	4	10																
4	4	10																
5	3	10																
6	4	10																
7	4	10																
8	4	10																
9	4	10																
10	4	10																
11	4	10																
12	3	10																
MEAN =			0.1	714.1	596.6	464.0	333.2	249.8	178.4	46.6	24.5	9.0	3.6	2.4	1.6	1.1	0.9	0.6	0.6
S.D. =			0.3	102.64	65.20	67.22	55.31	49.32	45.45	15.56	8.26	3.95	1.37	0.49	0.24	0.23	0.20	0.12	0.12

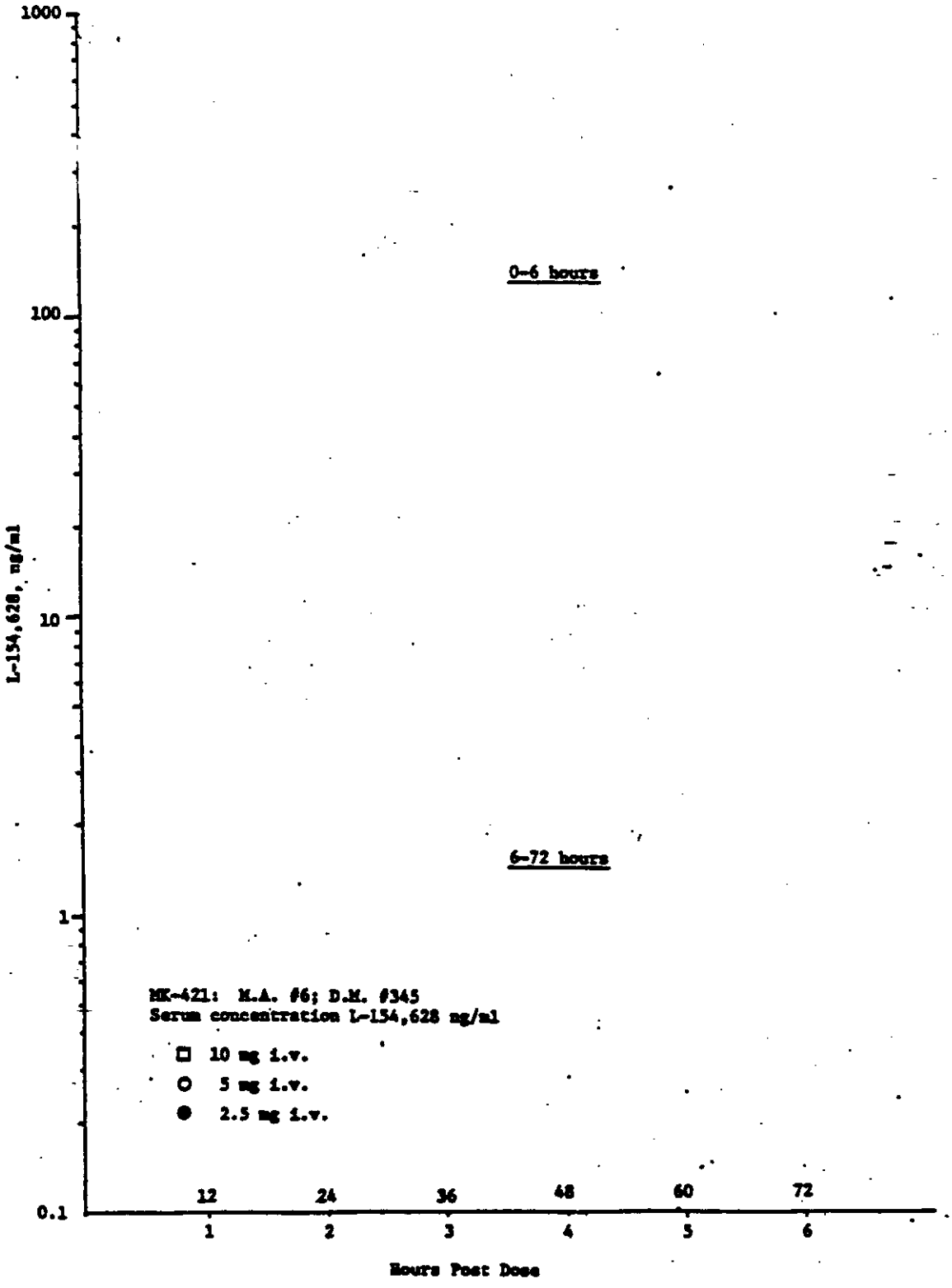
* INDICATES NO OR INSUFFICIENT SAMPLE

Study #6

MK-421
M.A. #6; D.M. #345

[redacted]

Table 6-7



Study #6

Table 6-8

MK421 STUDY #6, DM#345--URINARY EXCRETION

MICROGRAMS L-154,628 EXCRETED IN THE PERIODS SHOWN
TOTAL IN MILLIGRAMS

			HOURS										
SUB	PER	DOSE	PRE	0-1	1-2	2-4	4-6	6-8	8-24	24-36	36-48	48-72	72-96	96-120	TOTAL
1	2	0													
2	4	0													
3	3	0													
4	1	0													
5	4	0													
6	3	0													
7	1	0													
8	2	0													
9	3	0													
10	3	0													
11	2	0													
12	4	0													
1	1	2.5													
2	1	2.5													
3	1	2.5													
4	2	2.5													
5	1	2.5													
6	1	2.5													
7	2	2.5													
8	1	2.5													
9	2	2.5													
10	1	2.5													
11	1	2.5													
12	1	2.5													
		$\bar{x}$		1056	573	327	156	70	104						

			HOURS										
SUB	PER	DOSE	PRE	0-1	1-2	2-4	4-6	6-8	8-24	24-36	36-48	48-72	72-96	96-120	TOTAL
1	3	5													
2	2	5													
3	2	5													
4	3	5													
5	2	5													
6	2	5													
7	3	5													
8	3	5													
9	1	5													
10	2	5													
11	3	5													
12	2	5													
		$\bar{x}$													
1	4	10													
2	3	10													
3	4	10													
4	4	10													
5	3	10													
6	4	10													
7	4	10													
8	4	10													
9	4	10													
10	4	10													
11	4	10													
12	3	10													
		$\bar{x}$		4969	2127	1497	639	285	282						

Study #503

Table #503-1

Observed Maximum Serum Concentrations (C_{max}) of Total L-154,628, L-154,628 and MK-421 (by Difference), and Times (t_{max}) at Which They Occurred

Subject	Total L-154,628 (MK-422) C_{max} (ng/ml)	Total L-154,628 (MK-422) t_{max} (hours)	L-154,628 (MK-422) C_{max} (ng/ml)	L-154,628 (MK-422) t_{max} (hours)	MK-421 C_{max} (ng/ml)	MK-421 t_{max} (hours)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean (S.D.)	59.00 (± 21.5)	1.2	40.45 (± 17.5)	4 [$\bar{x}$ = 3.75] (±1.42)	48.80 (± 18.1)	1

Table #503-2

AUC_0^{72} (ng·hour/ml) for L-154,628 and L-154,826

Subject	L-154,628 (MK-422)	L-154,826
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Mean (S.D.)	490 (±152)	687 (±328)

Study #503

Urinary Recovery Expressed as Percent of Administered Dose of MK-421* and L-154,826

Table #503-3

Subject	Total L-154,628**	L-154,628	L-154,826
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean (S.D.)	61 (±12)	43 (±10.1)	29 (±14.6)

* Equivalent to 6.9 mg of L-154,628

** That which was excreted both as the free base of MK-421 and as the active diacid.

Table #503-4 Renal Clearances* (ml/min) of L-154,628 and L-154,826

Subject	L-154,628	L-154,826
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Mean (S.D.)	158 (±46)	106 (±13)

* Renal Clearance = $\frac{[\text{Urinary Recovery}]_{t}^{t'}}{AUC_{t}^{t'}}$

Study #503

Table 503-5

SERUM CONC. OF TOTAL DRUG, AS L-154,628,NG/ML

	HOURS															
SUBJ	0	0.25	0.5	1	1.5	2	3	4	6	8	10	24	48	72	96	AUC(0-72)
2																
5																
6																
7																
8																
10																
1																
3																
4																
9																
11																
12																
M=	0.52	1.65	28.92	52.26	51.55	47.93	44.48	38.82	28.74	21.72	16.13	4.12	1.56	0.98	0.96	559.3
S=	0.12	0.36	5.69	6.42	5.79	5.26	4.85	3.49	2.17	1.62	1.49	0.55	0.14	0.09	0.07	45.55

Table #503-6

SERUM CONC OF INTACT MK421, BY DIFFERENCE
EXPRESSED AS L-154,628, NG/ML.

	HOURS															
SUBJ	0	0.25	0.5	1	1.5	2	3	4	6	8	10	24	48	72	96	AUC(0-72)
2																
5																
6																
7																
8																
10																
1																
3																
4																
9																
11																
12																
M=	0.12	1.26	27.94	44.82	32.30	19.54	6.86	0.76	-0.31	-0.02	-0.86	0.11	0.07	0.05	0.01	68.8
S=	0.03	0.34	5.60	4.94	3.77	3.58	1.59	1.58	0.65	0.45	0.44	0.10	0.06	0.04	0.06	8.94

Study #503

Figure # 503-1

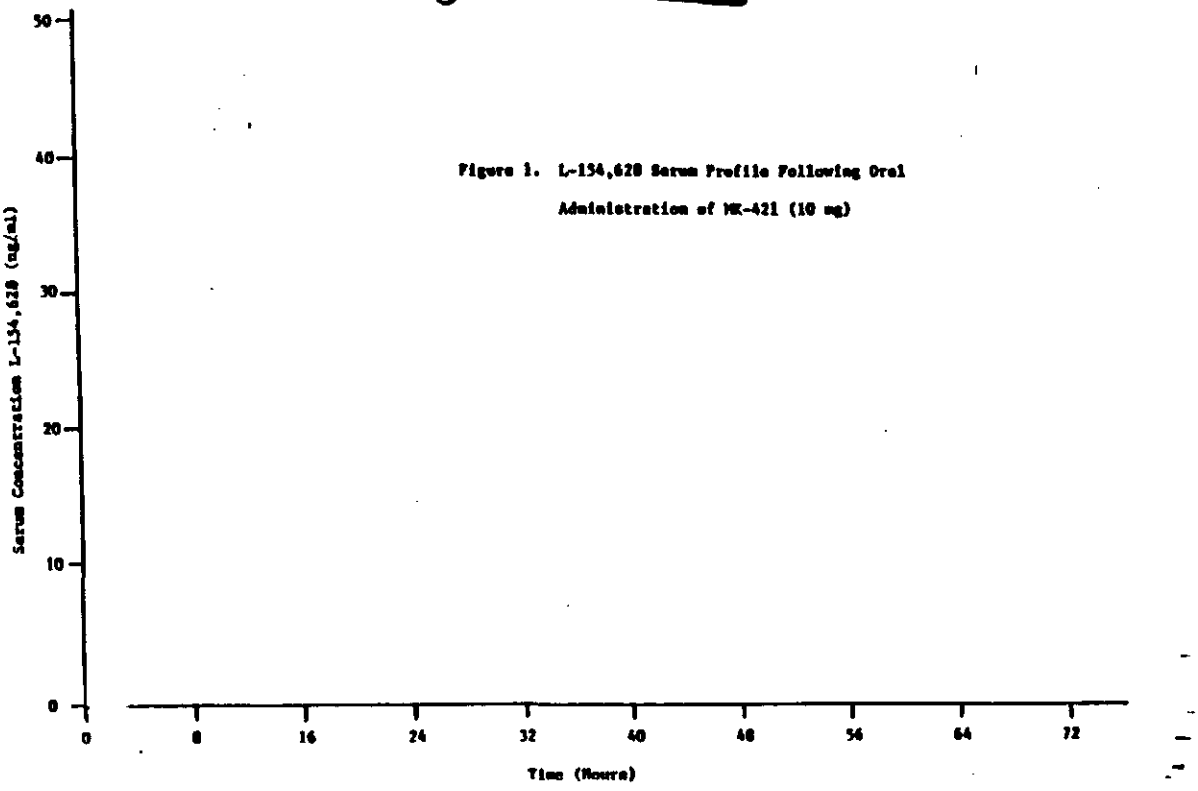


Figure 1. L-154,628 Serum Profile Following Oral Administration of MK-421 (10 mg)

Table # 503-7

SERUM CONC. OF L-154-628, NG/ML.

	HOURS															
SUBJ	0	0.25	0.5	1	1.5	2	3	4	6	8	10	24	48	72	96	AUC(0-72)
2																
5																
6																
7																
8																
10																
1																
3																
4																
9																
11																
12																
M=	0.40	0.40	0.98	7.45	19.24	28.40	37.62	38.06	29.05	21.73	16.99	4.01	1.49	0.93	0.95	490.5
S=	0.10	0.10	0.16	1.81	4.78	6.30	5.54	4.52	2.40	1.69	1.61	0.95	0.12	0.07	0.12	43.93

Study #503

Table #503-8

URINARY EXCRETION:L-154,628, MICROGRAM.

	HOURS								
SUBJ	0-2	2-4	4-6	6-8	8-20	10-24	24-48	48-72	TOTAL
2									
5									
6									
7									
8									
10									
1									
3									
4									
9									
11									
12									
M=	152	661	593	454	308	562	168	66	2970
S=	38	86	42	22	16	61	23	3	199

Table #503-9

URINARY EXCRETION:TOTAL DRUG AS MICROGM L-154,628.

	HOURS								
SUBJ	0-2	2-4	4-6	6-8	8-20	10-24	24-48	48-72	TOTAL
2									
5									
6									
7									
8									
10									
1									
3									
4									
9									
11									
12									
M=	932	1092	649	450	305	553	184	63	4234
S=	106	90	44	22	16	50	22	4	233

Study #518

Table 518-1

MK421: MA#518: DM#347

SERUM CONC. L-154,628, NG/ML.

DAY 1 ONLY. AUC TO 24HRS.

HOURS, DAY 1

SUB	PER	DOSE	0	0.5	1	2	3	4	6	8	12	15	22	24	AUC(0-24)
1	1	10													
2	1	10													
3	1	10													
4	1	10													
5	1	10													
6	1	10													
7	1	10													
8	1	10													
9	1	10													
10	1	10													
11	1	10													
12	1	10													
	MEAN=		0.0	1.1	7.2	27.6	33.7	34.1	26.0	17.8	7.8	6.2	2.9	2.4	

value included in mean

Table 518-2

MK421: MA#518: DM#347.

SERUM CONC. L-154,628, NG/ML.

DAY 8. AUC 0-24HRS DAY 8 ONLY.

HOURS POST DOSE (DAY 8)

SUB	PER	DOSE	0	0.5	1	2	3	4	6	8	12	15	22	24	AUC 0-24
1	1	10													
2	1	10													
3	1	10													
4	1	10													
5	1	10													
6	1	10													
7	1	10													
8	1	10													
9	1	10													
10	1	10													
11	1	10													
12	1	10													
	MEAN=		3.4	5.0	15.6	31.3	38.0	34.0	26.6	17.9	9.0	5.9	3.1	2.9	

Study # 518

Table 518-3

Urinary Recovery* of L-154,628 (mg) Following Administration of 10 mg MK-421, P.O.

Subject	Day 1	2	3	4	5	6	7	8
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	2.41	3.28	3.15	3.06	3.13	3.53	3.03	2.67

* For a dosing interval, i.e., 0-24 hours.

(-) Incomplete data.

Table 518-4

Minimum Serum Concentrations (C_{min})* of L-154,628 (ng/ml) for Each 10 mg Dose of MK-421

Subject	Dose 1	2	3	4	5	6	7	8
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	2.4	2.6	3.7 (3.1)**	3.0	3.6	3.1	3.4	2.9

* 24 hours post drug administration.

** Subject 10 omitted from mean.

Study # 518

[redacted]

Urinary Recovery* of L-154,628 Following
Administration of MK-421, P.O.

Table 518-5

Subject	Day 8 (0-24 hr) (%)	Total** (%)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Mean	39	45

* Expressed as percent of administered L-154,628 equivalents (based on dosage form assay values).

** From zero hour day 1 to 96 or 120 hrs (subjects 7, 11, 12) following last dose.

(-) Incomplete data.

Table 518-6

MK421: MA#518: DM#347

URINARY EXCRETION, L-154,628, MICROGMS(SUM =MGS).

DAY 8 ONLY.

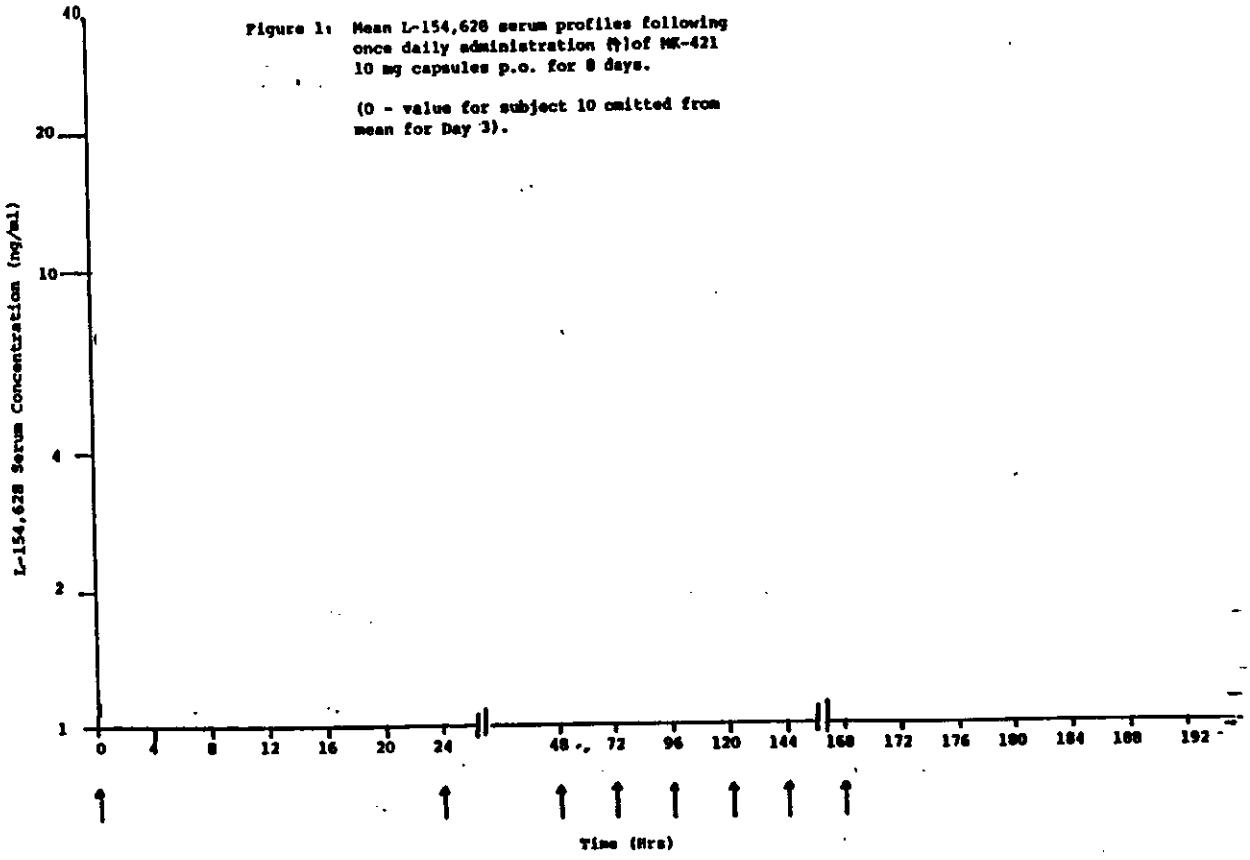
		HOURS POST DOSE DAY 8						
SUB	PER DOSE	0-1	1-2	2-4	4-8	8-12	12-24	SUM
1	1 10							
2	1 10							
3	1 10							
4	1 10							
5	1 10							
6	1 10							
7	1 10							
8	1 10							
9	1 10							
10	1 10							
11	1 10							
12	1 10							

Study # 518

Figure 518-1

Figure 1: Mean L-154,628 serum profiles following once daily administration of MK-421 10 mg capsules p.o. for 8 days.

(0 - value for subject 10 omitted from mean for Day 3).



APPEARS THIS WAY
ON ORIGINAL

Study #555

Table 555-1

Maximum Serum Concentrations, C_{max} (ng/ml), of Enalapril* and Times at Which They Occurred, T_{max} (hour), Following Oral Administration of 2.5, 10 and 40 mg Enalapril Maleate Capsules

Subject	Enalapril Maleate Capsules					
	2.5 mg		10 mg		40 mg	
	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	17.7	1.0	71.0	0.9	299.3	0.8

* Obtained by difference between total drug and MK-422 serum profiles

Table 555-2

Observed Maximum Serum Concentrations, C_{max} (ng/ml), of MK-422 and Times at Which They Were Observed, T_{max} (hour), Following Oral Administration of 2.5, 10 and 40 mg Enalapril Maleate Capsules

Subject	Enalapril Maleate Capsules					
	2.5 mg		10 mg		40 mg	
	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	5.9	6	32.3	4	149.8	3

Study #555

Table 555-3

$AUC_{0-\infty}$ (ng.hr/ml) for MK-422
Following Oral Administration of
2.5, 10 and 40 mg Enalapril Maleate Capsules

Subject	Enalapril Maleate Capsules 2.5 mg	10 mg	40 mg	RATIOS 10/2.5	40/2.5	40/10
1				—	—	—
2				—	—	—
3				—	—	—
4				—	—	—
5				—	—	—
6				—	—	—
7				—	—	—
8				—	—	—
9				—	—	—
10				—	—	—
11				—	—	—
12				—	—	—
Mean (S.D.)	158 (±37.5)	423 (±72)	1443 (±413.5)	2.7	— 9.1 —	3.4

Table 555-4

$AUC_{0-\infty}$, AUC^{E*} and $[AUC_{0-\infty} - AUC^{E}]$
(ng.hr/ml) for MK-422 Following I.V. Administration
of 5 mg MK-422

Subject	$AUC_{0-\infty}$	AUC^{E}	$[AUC_{0-\infty} - AUC^{E}]$
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	767	125	642
Predicted Mean (from regression lines, Figure 4)	719	107**	612

* AUC^{E} = Area under the terminal phase of the serum profile extrapolated from time zero to infinity.

** Equivalent to the vertical distance between the parallel lines (i.e., the intercept).

Study #555

Total Urinary Recovery of Total Drug[a] Following Oral Administration of 2.5, 10 and 40 mg Enalapril Maleate Capsules

TABLE 555-5

Subject	Enalapril Maleate Capsule 2.5 mg	10 mg	40 mg
1			
2			
3			
4[b]			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	46	52	53
S.D. (S)	±7.69 (16.7)	±12.3 (24%)	±16.8 (32%)

[a] Expressed as percent of administered MK-422 equivalents (based on PR&D assay values) and rounded to nearest percent.
[b] Omitted from mean.
[c] Missing data

Table 555-6

Total Urinary Recovery of MK-422[a] Following Oral Administration of 2.5, 10 and 40 mg Enalapril Maleate Capsules and I.V. Administration of 5 mg MK-422

Subject	Enalapril Maleate Capsules 2.5 mg	10 mg	40 mg	MK-422 I.V. 5 mg
1				
2				
3				
4[c]				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	28	33	36	92
S.D. (S)	± 8.65 (31%)	± 9.16 (28%)	± 13.3 (37%)	± 3.36 (3.6%)

[a] Expressed as percent of administered MK-422 equivalents (based on PR&D assay values) and rounded to nearest percent.
[b] Omitted from mean.
[c] Omitted from mean for oral treatments.
[d] Missing data.

Study #555

Table 555-7

Enalapril Maleate 2.5, 10, 40mg Capsules

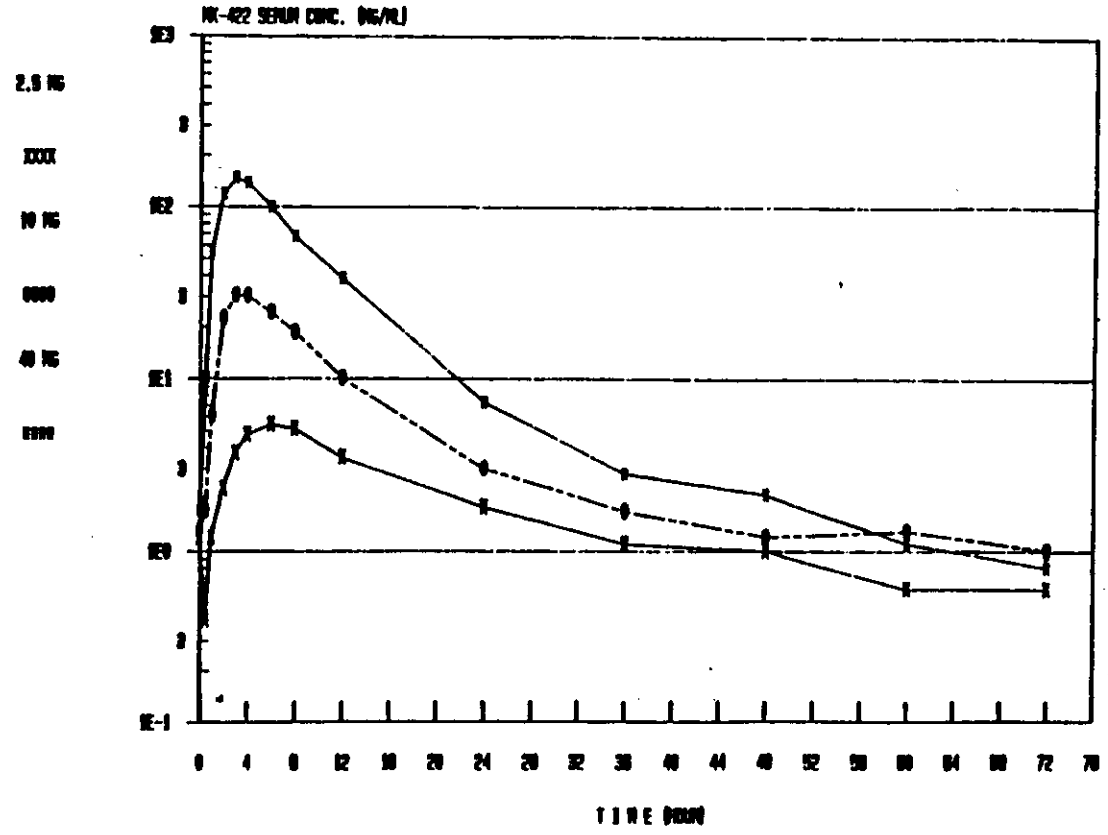
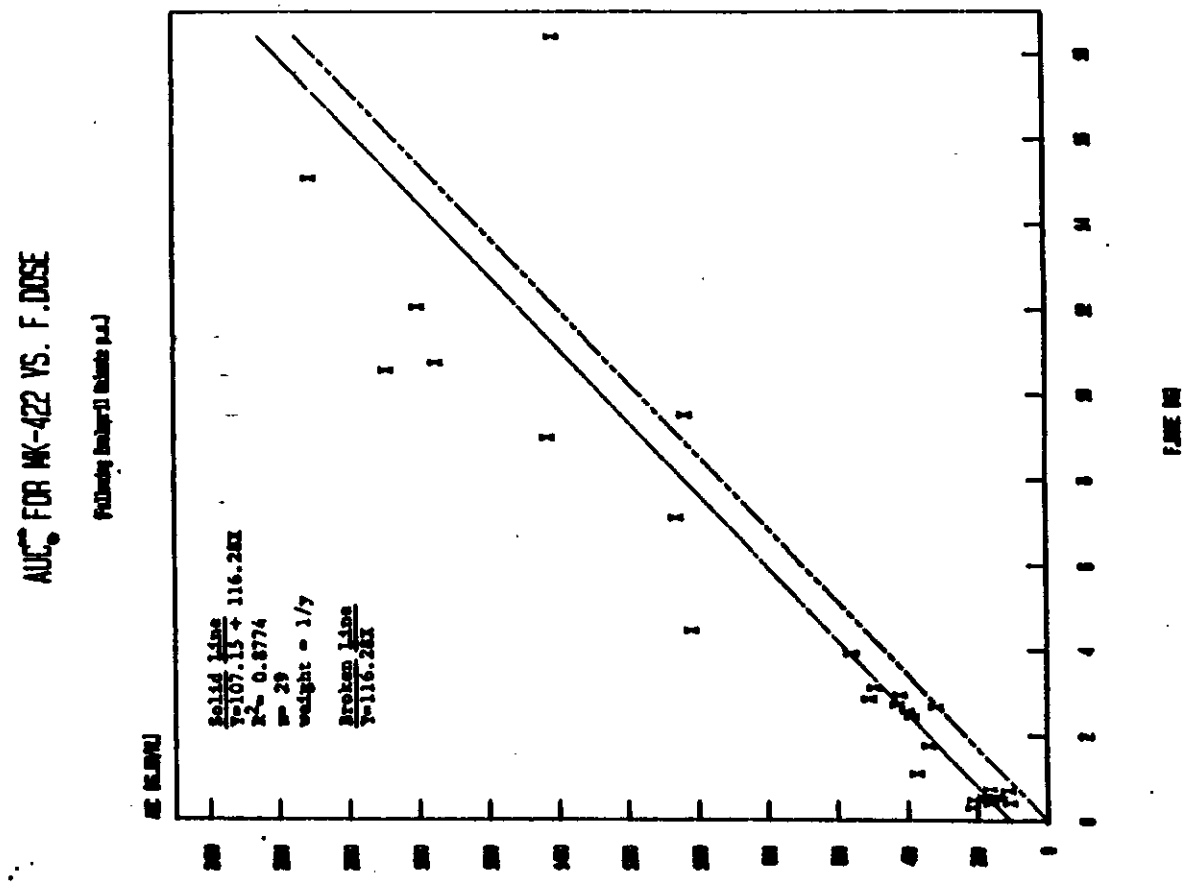


Table 555-8



Enalapril Maleate
D.M. #384, M.A. #555

Study #555

Table 555-9

Ratio of MK-422/Total Drug[a] for Total Urinary Recovery
of Drug Following Oral Administration of
2.5, 10 and 40 mg Enalapril Maleate Capsules

Subject	Enalapril Maleate Capsules		
	2.5 mg	10 mg	40 mg
1			
2			
3			
4[b]			
5			
6			
7			
8			
9			
10			
11.			
12			
Geometric Mean	.58	.62	.65

[a] Calculated from actual mg recovered.
[b] Omitted from mean.
[c] Missing data

MK-421
Study No. 110
Dr. Lowenthal

Figure 110-1

Mean Serum Profiles of Enalaprilic Acid (EA)
Following Oral Administration of Enalapril Maleate
to Patients with Severe Renal Insufficiency (Group 1)
and Moderate Renal Insufficiency (Group 2),
and Subjects with Normal Renal Function (Group 3)

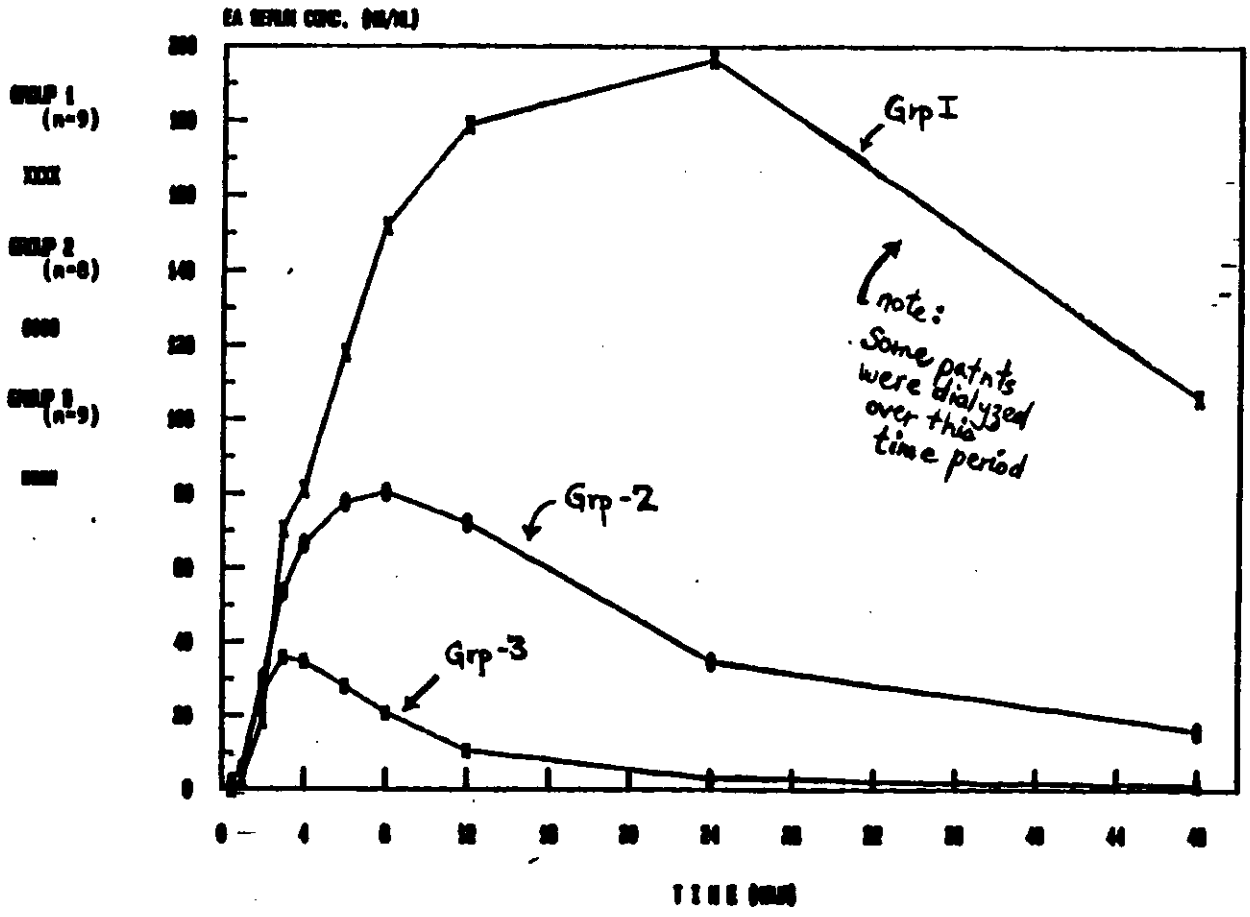


Table 110-1

AREA UNDER THE ENALAPRILIC ACID PLASMA CURVE FOR 0 TO 6 HOURS FOLLOWING ENALAPRIL MALEATE ADMINISTRATION--GROUP 1--SEVERE RENAL INSUFFICIENCY

Revised 7/25/83

Patient	AUC 0-6 Hours (ng.h/ml) Without Dialysis	With Dialysis**
1A		
1B		
1C		
1D		
1E		
1F		
1G		
1H		
1I		
1J		
Median[1]	321	149

**AUC--0 to 6 hours--significantly lower than during enalapril maleate therapy without dialysis, p<.01.

[1]Excludes Patient 1I.

NOTE: Patients were dialyzed for four hours beginning one hour after drug administration.

Table 110-2

AREA UNDER THE ENALAPRILIC ACID SERUM CURVE FOR 0 TO 48 HOURS FOLLOWING ENALAPRIL MALEATE ADMINISTRATION--GROUPS 2 & 3

GROUP 2 Mild to Moderate Renal Insufficiency		GROUP 3 Normals	
Patient	AUC 0-48 Hours (ng.h/ml)	Patient	AUC 0-48 Hours (ng.h/ml)
2A		3A	
2B		(3B	
2C		3C	
2D		3D	
2F		3E	
2G		3F	
2H		3G	
2I		3H	
		3I	
		3J	
Mean	1986**	Mean[1]	409
S.D.	1430	S.D.	96
95% C.I.	(790, 3181)	95% C.I.	(335, 483)
Moderate Insufficiency[2]			
Mean	2497**		
S.D.	1267		
95% C.I.	(1167, 3828)		

[1] Excluding Patient 3B.
[2] Excluding Patients 2A and 2C.
** Significantly greater than normals, p<.01.

Study # 110

Table 110-3

ZERO TO FORTY-EIGHT HOUR URINARY RECOVERY[1] OF ENALAPRILIC ACID AND TOTAL DRUG[2] FOLLOWING ORAL ADMINISTRATION OF ENALAPRIL MALEATE--GROUPS 2 & 3

Mild to Moderate Renal Insufficiency				Normals			
Patient	E.A.	Total Drug (TD)	E.A./TD	Patient	E.A.	Total Drug (TD)	E.A./TD
2A				3A			
2B				3B			
2C				3C			
2D				3D			
2F				3E			
2G				3F			
2H				3G			
2I				3H			
				3I			
				3J			
Mean	30	38**	.82**	Mean[4]	40	62	.64
S.D.	13	17	-	S.D.	5	8	-
95% C.I.	(19,41)	(24,52)	(.71,.95)	95% C.I.	(36,44)	(57,68)	(.58,.71)
Moderate Only[3]							
Mean	30	35**	.89**				
S.D.	15	19	-				
95% C.I.	(14,46)	(15,55)	(.81,.97)				

1 Percent of administered enalaprilic acid equivalents.

2 Enalaprilic acid measured after sample hydrolysis, representing that which was in the sample as enalaprilic acid itself and that which was present as enalapril.

3 Excluding Patients 2A and 2C.

4 Excluding Patient 3B.

** Significantly different from normals, $p<.01$.

E.A. Enalaprilic Acid.

Study # 110

Dr. D. T. Lowenthal
MK-421

VII-01084

Study #110

Table 110-4

URINARY EXCRETION RATE OF ENALAPRILIC ACID (μg/h) FOLLOWING ORAL ADMINISTRATION OF ENALAPRIL MALEATE--GROUPS 2 & 3

Patient	Mild to Moderate Renal Insufficiency - Time Period (h) 0-4	4-8	8-12	12-24	24-48	Patient	Normals - Time Period (h) 0-4	4-8	8-12	12-24	24-48
2A						3A					
2B						3B					
2C						3C					
2D						3D					
2F						3E					
2G						3F					
2H						3G					
2I						3H					
						3I					
						3J					
Mean	55**	112**	80	63	17	Mean[3]	186	228	122	39	6.8
S.D.	57	55	54	37	13	S.D.	88	36	38	12	3.9
95% C.I.	(3,108)	(61,163)	(30,130)	(32,93)	(6,27)	95% C.I.	(118,254)	(200,255)	(93,151)	(30,48)	(3.8,9.8)
Moderate Only[2]											
Mean	24**	94**	78	69*	20*						
S.D.	18	45	54	41	12						
95% C.I.	(1,47)	(38,150)	(11,146)	(27,112)	(7,33)						

Revised 7/1/83

1 0-12 hour sample, not included in mean.
2 Excluding Patients 2A and 2C.
3 Excluding Patient 3B.
*,** Significantly different from normals, $p<.05$, $p<.01$, respectively.

NOTE: NV = no void.
<LNT = below assay limit, considered to be zero.

Table 110-5

URINARY EXCRETION RATE OF TOTAL DRUG (ENALAPRILIC ACID AFTER SAMPLE HYDROLYSIS) (μg/h) FOLLOWING ORAL ADMINISTRATION OF ENALAPRIL MALEATE--GROUPS 2 & 3

Patient	Mild to Moderate Renal Insufficiency - Time Period (h) 0-4	4-8	8-12	12-24	24-48	Patient	Normals - Time Period (h) 0-4	4-8	8-12	12-24	24-48
2A						3A					
2B						3B					
2C						3C					
2D						3D					
2F						3E					
2G						3F					
2H						3G					
2I						3H					
						3I					
						3J					
Mean	168**	140**	87	63	17	Mean[3]	545	251	127	39	6.8
S.D.	166	67	60	37	13	S.D.	160	39	42	12	3.9
95% C.I.	(15,321)	(78,202)	(32,143)	(32,93)	(6,27)	95% C.I.	(424,670)	(221,281)	(95,159)	(30,48)	(3.8,9.8)
Moderate Only[2]											
Mean	77**	124**	87	69*	20*						
S.D.	63	67	63	41	12						
95% C.I.	(-2,155)	(41,207)	(9,166)	(27,112)	(7,33)						

Revised 7/1/83

1 0-12 hour sample, not included in mean.
2 Excluding Patients 2A and 2C.
3 Excluding Patient 3B.
*,** Significantly different from normals, $p<.05$, $p<.01$, respectively.

NOTE: NV = no void.
<LNT = below assay limit, considered to be zero.

Study #168

Observed Maximum Serum Concentrations (C_{max})* for Enalaprilic Acid and the Times They Were Observed (T_{max})** Following Oral Administration of 5, 10, 20, and 40 mg Enalapril Maleate Tablets and I.V. Administration of Enalapril Maleate (5 mg)

Table 168-4

Subject	Tablets 5 mg C_{max}	Tablets 5 mg T_{max}	Tablets 10 mg C_{max}	Tablets 10 mg T_{max}	Tablets 20 mg C_{max}	Tablets 20 mg T_{max}	Tablets 40 mg C_{max}	Tablets 40 mg T_{max}	Enalapril Maleate I.V. C_{max}	Enalapril Maleate I.V. T_{max}
1										
2										
3										
4										
5										
6***										
7										
8										
9										
10										
Mean	15.3	4.8	37.4	3.9	70.8	3.2	123.1	3.4	16.5	4.0
(S.D.)	(6.3)		(17)		(33.8)		(41.7)		(4.5)	
(C.V.) %	(41.2)		(45.4)		(48)		(34)		(27)	

* ng/ml
** hours
*** Excluded from mean

Table 168-5 $AUC_{0-\infty}$ (ng.hr/ml) for Enalaprilic Acid Following Oral Administration of 5, 10, 20, and 40 mg Enalapril Maleate Tablets and I.V. Administration of Enalapril Maleate (5 mg) and Enalaprilic Acid

Subject	Tablets 5 mg	Tablets 10 mg	Tablets 20 mg	Tablets 40 mg	Intravenous Solution Enalapril Maleate	Intravenous Solution Enalaprilic Acid
1						
2						
3						
4						
5						
6*						
7						
8						
9						
10						
Mean	255	440	731	1331	270	652
S.D.	(28.9)	(41.5)	(121.8)	(249.5)	(62.7)	(95.2)
C.V. %	(11.3)	(9.4)	(16.7)	(18.7)	(23.2)	(14.6)

* Excluded from mean

Table 168-6

Absorption of Drug* Following Oral Administration of 5, 10, 20, and 40 mg Enalapril Maleate Tablets

Subject	Tablets 5 mg	10 mg	20 mg	40 mg
1				
2				
3				
4				
5				
6**				
7				
8				
9				
10				
Geometric Mean	.63	.73	.62	.59
Arith Mean (S.D.)	0.64 (±.15)	0.74 (0.15)	0.64 (0.18)	0.61 (.16)

* As estimated from dose-adjusted urinary recovery of total drug (enalaprilic acid measured after hydrolysis), tablets to total drug, enalapril maleate i.v.

** Excluded from mean. (Low values reflect abnormally low urinary recoveries for the tablets compared to relatively normal recovery for enalapril maleate i.v.)

Study #168

Table 168-7

Bioavailability* of Enalaprilic Acid from 5, 10, 20, and 40 mg Tablets and Enalapril Maleate I.V.

Subject	Tablets 5 mg	10 mg	20 mg	40 mg	Enalapril Maleate i.v.
1					
2					
3					
4					
5					
6**					
7					
8					
9					
10					
Geometric Mean	.38	.44	.38	.36	.43
Arith. mean (S.D.)	.39 (.11)	.45 (.09)	.39 (.11)	.37 (.11)	.43 (.06)

* As estimated from the dose-adjusted urinary recovery ratio of enalaprilic acid for the enalapril maleate formulations to enalaprilic acid i.v.

** Excluded from the mean.

*** Reflects abnormally low urinary recovery for enalaprilic acid i.v.

study #168

Table 168-8

Extent of Hydrolysis of Enalapril to Enaprilic Acid
(Estimated from the Ratio of Bioavailability/Absorption)
Following Oral Administration of 5, 10, 20, and 40 mg
Enalapril Maleate Tablets

Subject	Tablets			
	5 mg	10 mg	20 mg	40 mg
1				
2				
3				
4				
5				
6*				
7				
8				
9				
10				
Geometric Mean	.60	.61	.62	.61

* Excluded from mean. These values are artifically high due to the combined effect of abnormally low urinary recoveries for enalapril maleate p.o. and enalaprilic acid i.v., and relatively normal recovery for enalapril maleate i.v.

Arith mean (S.D.)	0.60 (.05)	0.61 (.06)	0.62 (0.066)	0.61 (0.06)
C.V.	8.3%	9.8%	10.6%	9.8%

Study #168

Table 168-9

Total Urinary Recovery* of Total Drug** Following Oral Administration of 5, 10, 20, and 40 mg Enalapril Maleate Tablets and 5 mg Enalapril Maleate I.V.

Subject	Tablets				Enalapril Maleate i.v.
	5 mg	10 mg	20 mg	40 mg	
1					
2					
3					
4					
5					
6***					
7					
8					
9					
10					
Mean	56	65	56	53	86

* Percent of administered enalaprilic acid equivalents
** Enalaprilic acid measured after hydrolysis
*** Excluded from mean

Table 168-10

Total Urinary Recovery* of Enalaprilic Acid Following Oral Administration of 5, 10, 20, and 40 mg Enalapril Maleate Tablets and 5 mg Enalapril Maleate and Enalaprilic Acid I.V.

Subject	Tablets				Intravenous Solution	
	5 mg	10 mg	20 mg	40 mg	Enalapril Maleate	Enalaprilic Acid
1						
2						
3.						
4						
5						
6**						
7						
8						
9						
10						
Mean	35	41	36	34	39	90

* Percent of administered enalaprilic acid equivalents
** Excluded from mean.

Study #168

Table 168-11

Bioavailability – Mean Serum Parameters for Enalaprilic Acid

Variable	Treatment	N	Mean	S.D.	95% Con. Int.	ANOVA - P Treatment Effect	Multiple Comparisons
AUC 0 - ∞ (ng.h/ml)	A = 5 mg E.M. tablet	9	254.6	28.9	(232.3, 276.8)	p<.01	A<B<C<D, p<.01
	B = 10 mg E.M. tablet	9	439.9	41.6	(408.0, 471.8)		F<B<C<D, p<.01
	C = 20 mg E.M. tablet	9	731.1	121.8	(637.6, 824.6)		
	D = 40 mg E.M. tablet	9	1330.7	249.6	(1138.9, 1522.6)		
	F = 5 mg E.M. I.V.	9	270.4	62.8	(222.2, 318.7)		
AUC 0 - ∞ (ng.h/ml) Dose Adjusted (a)	A = 5 mg E.M. tablet	9	254.6	28.9	(232.3, 276.8)	p<.01	A>C, A>D p<.01
	B = 10 mg E.M. tablet	9	219.9	20.8	(204.0, 235.9)		B>D p<.05
	C = 20 mg E.M. tablet	9	182.8	30.5	(159.4, 206.2)		
	D = 40 mg E.M. tablet	9	166.3	31.2	(142.4, 190.3)		
	F = 5 mg E.M. I.V.	9	270.4	62.8	(222.2, 318.7)		F>D, F>C, F>D, p<.01
Observed Maximum Serum Concentration (ng/ml)	A = 5 mg E.M. tablet	9	15.3	6.3	(10.4, 20.1)	p<.01	A<B<C<D, p<.01
	B = 10 mg E.M. tablet	9	37.4	17.8	(24.4, 50.5)		F<B<C<D, p<.01
	C = 20 mg E.M. tablet	9	70.8	33.8	(44.9, 96.8)		
	D = 40 mg E.M. tablet	9	121.1	41.7	(91.8, 150.2)		
	F = 5 mg E.M. I.V.	9	16.5	4.6	(13.1, 20.0)		
Observed Maximum Serum Concentration (ng/ml) Dose Adjusted (a)	A = 5 mg E.M. tablet	9	15.3	6.3	(10.4, 20.1)	p>.2	No significant differences
	B = 10 mg E.M. tablet	9	18.7	8.5	(12.2, 25.2)		
	C = 20 mg E.M. tablet	9	17.7	8.4	(11.2, 24.2)		
	D = 40 mg E.M. tablet	9	15.3	5.2	(11.4, 19.4)		
	F = 5 mg E.M. I.V.	9	16.5	4.6	(13.1, 20.0)		
Time to Observe Maximum Serum Concentration (hours)	A = 5 mg E.M. tablet	9	4.8	1.8	(3.4, 6.2)	p=.07	A>C, A>D p<.05
	B = 10 mg E.M. tablet	9	3.9	0.9	(3.2, 4.6)		
	C = 20 mg E.M. tablet	9	3.2	0.7	(2.7, 3.7)		
	D = 40 mg E.M. tablet	9	3.4	0.7	(2.9, 4.0)		
	F = 5 mg E.M. I.V.	9	4.8	1.7	(2.7, 6.3)		

(a) Adjusted to 5 mg: value at actual dose x $\frac{5\text{ mg}}{\text{Actual Dose}}$

Table 168-12

Bioavailability – Mean Urine Parameters

Variable	Treatment	N	Mean	S.D.	95% Con. Int.	ANOVA - P Treatment Effect
Total Urinary Recovery of Enalaprilic Acid (% of administered E.A. equivalents)	5 mg E.M. tablet	9	35.2	9.5	(27.9, 42.5)	p=.19
	10 mg E.M. tablet	9	41.2	9.4	(34.0, 48.5)	
	20 mg E.M. tablet	9	35.6	10.8	(27.3, 43.9)	
	40 mg E.M. tablet	9	34.0	10.1	(26.2, 41.8)	
	5 mg E.M. I.V.[3]	9	39.1	4.8	35.4, 42.8)	
	5 mg E.A. I.V.[3]	9	90.3	10.9	(81.9, 98.7)	
Total Urinary Recovery of Total Drug[1] (% of administered E.A. Equivalents)	5 mg E.M. tablet	9	55.8	13.3	(45.6, 66.0)	.06
	10 mg E.M. tablet	9	64.7	15.4	(52.9, 76.5)	
	20 mg E.M. tablet	9	55.6	16.9	(42.5, 68.6)	
	40 mg E.M. tablet	9	52.6*	13.8	(42.0, 63.1)	
	5 mg E.M. I.V.[3]	9	86.1	5.3	(82.1, 90.2)	
Bioavailability of[2] Enalapril Acid (Dose adjusted urinary recovery ratio of E.A. for E.M. doses to E.A. I.V.)	5 mg E.M. tablet	9	0.38	--	(0.30, 0.48)	>.2
	10 mg E.M. tablet	9	0.44	--	(0.37, 0.53)	
	20 mg E.M. tablet	9	0.38	--	(0.30, 0.48)	
	40 mg E.M. tablet	9	0.36	--	(0.29, 0.45)	
	5 mg E.M. I.V.	9	0.43	--	(0.39, 0.48)	
Absorption of Drug[2] (Dose-adjusted urinary recovery of total drug[1], tablets to total drug[1] E.M. I.V.	5 mg E.M. tablet	9	0.63	--	(.51, .78)	.06
	10 mg E.M. tablet	9	0.73	--	(.61, .87)	
	20 mg E.M. tablet	9	0.62*	--	(.49, .78)	
	40 mg E.M. tablet	9	0.59*	--	(.48, .73)	
Extent of Hydrolysis[2] of E.M. to E.A. (Bioavailability/ Absorption)	5 mg E.M. tablets	9	0.60	--	(0.56, 0.65)	>.2
	10 mg E.M. tablets	9	0.61	--	(0.57, 0.66)	
	20 mg E.M. tablets	9	0.62	--	(0.57, 0.67)	
	40 mg E.M. tablets	9	0.61	--	(0.57, 0.66)	

[1] Total Drug = Enalaprilic Acid measured after hydrolysis
[2] Mean reported is geometric mean
[3] Not included the Analysis of Variance
*Significantly differently from 10 mg dose, p<.05)

A160

Table 168-13

[redacted]

$AUC_{0-\infty}$ (ng·h/ml) for Enalaprilic Acid Following Oral Administration of 5, 10, 20 and 40 mg Enalapril Maleate Tablets and I.V. Administration of Enalapril Maleate (5 mg) and Enalaprilic Acid (5 mg)

Subject	Tablets				Intravenous Solution	
	5 mg	10 mg	20 mg	40 mg	Enalapril Maleate	Enalaprilic Acid
1						
2						
3						
4						
5						
6*						
7						
8						
9						
10						
Mean	255	440	731	1331	270,(284)[P1]	652,(606)[P2]
					$[AUC_{0-\infty}-AUC^{E}]$**	524,(478)[P3]

* Excluded from mean

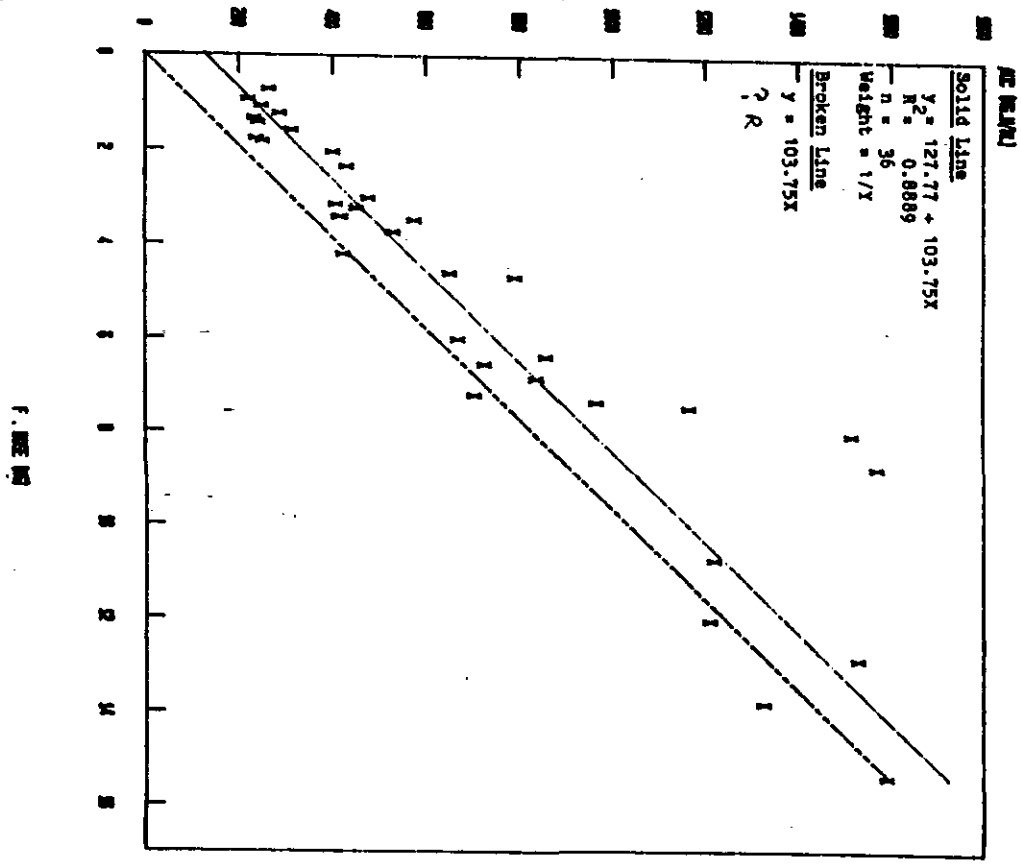
** Mean residual area, where AUC^{E} is the area under the terminal phase of the serum profile extrapolated from zero to infinity

P1 Value predicted from Figure 1: y=127.77 + 103.75X, where X=mean bioavailability of enalaprilic acid (Table 5) times dose.

P2 Value predicted from Figure 1: y=127.77 + 103.75X, where X=mean urinary recovery of enalaprilic acid (Table 3) times dose.

P3 Value predicted from Figure 1: y=103.75X, where X=mean urinary recovery of enalaprilic acid (Table 3) times dose.

Figure 168-1



[redacted] Relationship of $AUC_{0-\infty}$ for Enalaprilic Acid to the Bioavailability of Enalaprilic Acid Following Oral Administration of 5, 10, 20 and 40 mg Enalapril Maleate Tablets

Study #53

Table 53-1

Parameter	Treatment	N[a]	Mean	Standard Deviation	95% Confidence Interval
Observed maximum MK-422 serum concentration (ng/ml)	Tablet	11	45.1	16.2	(34.2, 56.0)
	Capsule	11	37.5	13.5	(28.4, 46.6)
Time to observed maximum MK-422 serum concentration (hr)	Tablet	11	3.9	1.1	(3.2, 4.6)
	Capsule	11	3.6	1.0	(2.9, 4.3)
Observed maximum MK-421 serum concentration (ng/ml)	Tablet	10[b]	67.3	15.8	(56.0, 78.6)
	Capsule	11	69.3	34.1	(46.4, 92.2)
Time to observed maximum MK-421 serum concentration (hr)	Tablet	10[b]	1.1	.5	(0.7, 1.5)
	Capsule	11	1.0	.4	(0.7, 1.3)
AUC_0^{72} (ng.hr/ml) for MK-422	Tablet	11	457.2	80.5	(403.1, 511.3)
	Capsule	11	436.3	112.5	(360.7, 511.9)
Urinary recovery of MK-422 (% of administered MK-422 equivalents)	I.V.	11	106.1	15.1	(96.0, 116.2)
	Tablet	11	40.3	8.2	(34.8, 45.8)
	Capsule	11	41.9	9.7	(35.4, 48.4)
Urinary recovery of total drug (% of administered MK-422 equivalents)	Tablet	11	62.8	8.9	(56.8, 68.8)
	Capsule	11	60.9	12.3	(52.6, 69.2)
Urinary recovery ratio of MK-422 to total drug	Tablet	11	.65[c]	--	(.60, .70)
	Capsule	11	.68[c]	--	(.64, .72)

(a) Subject #2 excluded due to missing data from one of the treatment periods.
(b) Data not available for Patient #10.
(c) Geometric mean.

Table 53-2

[redacted]

Power of Detecting Differences Between Capsules and Tablets at the $\alpha = .05$ Significance Level For Urinary Recovery of MK-422 and Total Drug As Percent of Administered MK-422 Equivalents

	Detectable Difference				
	10%	15%	20%	25%	30%
MK-422	.22	.45	.71	.90	.98
Total drug	.20	.40	.65	.86	.96

study # 53

Table 53-3

Individual and Mean Peak Serum Concentration, C_{max} (ng/ml) of MK-421 and Time of Peak Serum Concentration, T_{max} (hour) of MK-421 in Serum of Subjects Following Oral Administration of 10 mg MK-421 Capsules and 10 mg MK-421 Tablets

Subject	Tablet		Capsule	
	C_{max} (ng/ml)	T_{max} (hr)	C_{max} (ng/ml)	T_{max} (hr)
1				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	67.3	1	69.3	1

*Obtained as the difference in MK-422 equivalents before and after sample hydrolysis.

Table 53-4

Individual and Mean Peak Serum Concentration, C_{max} (ng/ml) of MK-422, and Time of Peak Serum Concentration, T_{max} (hour) of MK-422 in Serum of Subjects Following Oral Administration of 10 mg MK-421 Capsules and 10 mg MK-421 Tablets

Subject	Tablet		Capsule	
	C_{max} (ng/ml)	T_{max} (hr)	C_{max} (ng/ml)	T_{max} (hr)
1				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	45.1	4	37.5	4

Study #53

Table 53-5

Individual and Mean Areas Under the MK-422 Serum Concentration-Time Curves (AUC_{0-72}) for the 10 mg MK-421 Tablet (Treatment B) and the 10 mg MK-421 Capsule (Treatment C)

Subject	Tablet	Capsule	Ratio Cap/Tab
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	457	436	8/11 PASS (73%

75/75 Evaluation

Table 53-6

Urinary Recovery Ratios of MK-422 to Total Drug Following Oral Administration of MK-421 Tablets and Capsules

Subject	Tablet (MK-422/Total Drug)	Capsule (MK-422/Total Drug)	Ratio Cap/Tab
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Geometric Mean	.65	.68	10/11 PASS

75/75 Evaluation

Study #53

Table 53-7

Individual and Mean Concentrations (ng/ml) of MK-422 in Serum of Subjects Given the 10 mg MK-421 Tablet (Treatment B) and the 10 mg MK-421 Capsule (Treatment C)

SUB	PER	DOSE	0	0.5	1	2	3	4	6	8	12	24	48	72HR
1	1	B												
3	2	B												
4	3	B												
5	3	B												
6	1	B												
7	2	B												
8	3	B												
9	1	B												
10	1	B												
11	3	B												
12	2	B												
	MEAN=		0.0	1.4	5.3	24.2	42.7	39.9	32.8	24.5	11.0	3.0	1.2	0.8
1	3	C												
3	3	C												
4	2	C												
5	1	C												
6	2	C												
7	1	C												
8	2	C												
9	3	C												
10	2	C												
11	1	C												
12	3	C												
	MEAN=		0.0	1.4	6.0	26.4	34.8	35.7	31.3	22.4	11.1	3.2	1.4	0.7

Table 53-8

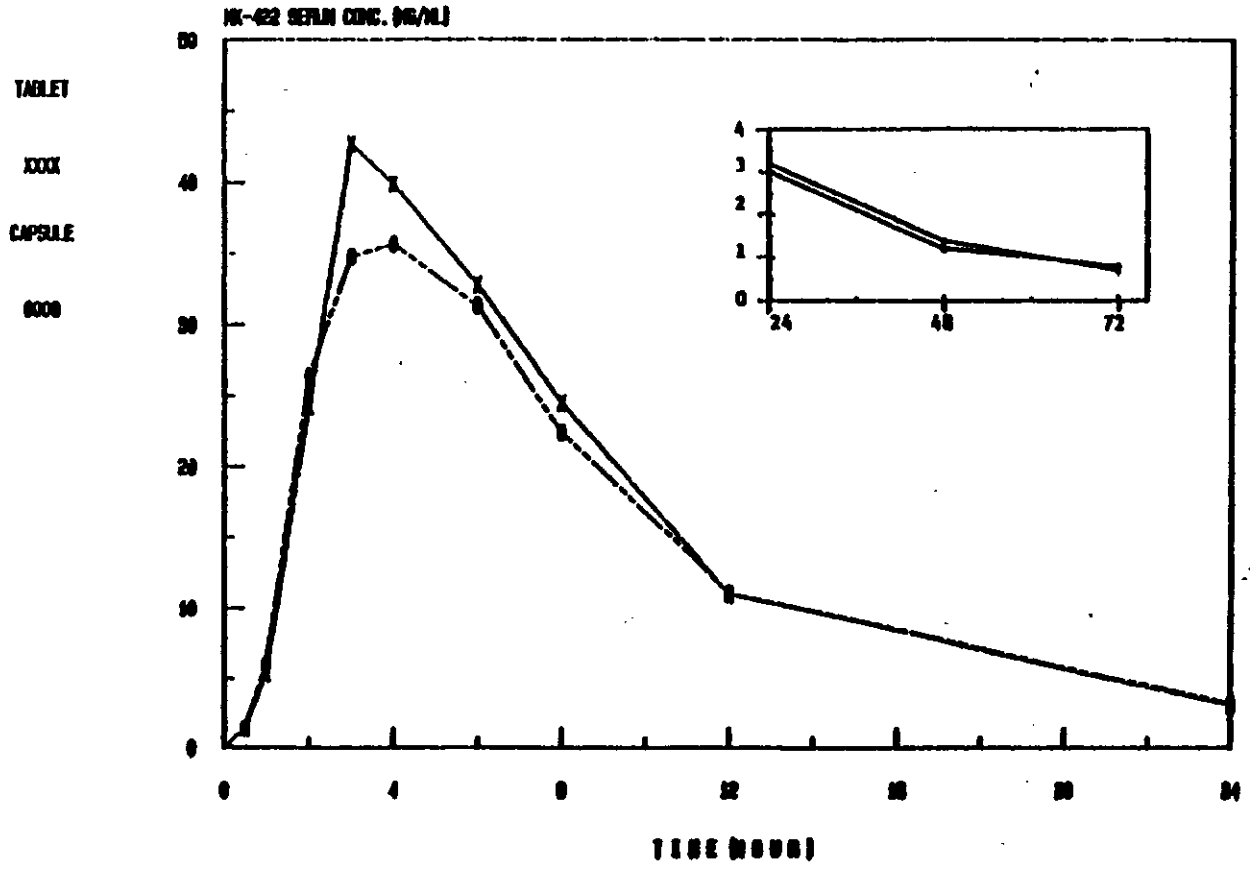
Individual and Mean Concentrations (ng/ml) of MK-422 in Serum of Subjects Given the 5 mg MK-422 Intravenous Dose (Treatment A)

SUB	PER	DOSE	0	10'	20'	30'	1	1.5	2	4	6	8	12	24	48	72HR
1	2	A														
3	1	A														
4	1	A														
5	2	A														
6	3	A														
7	3	A														
8	1	A														
9	2	A														
10	3	A														
11	2	A														
12	1	A														
	MEAN=		0.0	301.5	230.7	213.3	146.3	101.4	76.7	28.0	11.9	6.5	3.3	1.7	1.2	0.8

Study #53

Figure 53-1

Mean MK-422 Serum Profiles Following Oral Administration of 10 mg MK-421 Tablets and 10 mg MK-421 Capsules



Total Drug - Urinary Excretion (from table 9, p 1388, vol 3.336)

Sum (0-96 hours) in mg.

Subject	Tablet	Capsule	Ratio Cap/Tab	
1	5.73	4.61	0.8	
3	3.67	4.22	1.15	
4	3.97	5.12	1.29	– Fail
5	4.11	3.65	0.89	
6	4.23	2.02	0.48	– Fail
7	4.24	3.97	0.94	
8	4.34	4.32	0.99	
9	5.14	4.72	0.92	
10	4.16	4.44	1.07	
11	4.80	3.97	0.83	
12	3.67	4.88	1.33	– Fail

8/11 PASS (72.7%)

75/75 Eval

Study #523

Table 523-3

Ratios of Urinary Recoveries of L-154,628 and Total Drug for Oral Administration of MK-421 Capsules to L-154,628 for I.V. L-154,628 Administration

Subject	L-154,628 $(B/A)^*$ (Availability)	Total Drug $(C/A)^*$ (Absorption)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Geometric Mean	.54	.74

* see table below

(-) Incomplete Data

Table 523-4

Urinary Recovery* of L-154,628 Following Administration of L-154,628 I.V. and Recovery of L-154,628 and Total Drug Following Oral Administration of MK-421 Capsules

Subject	L-154,628 I.V. L-154,628 (A)	MK-421 Capsules, P.O. L-154,628 (B)	MK-421 Capsules, P.O. Total Drug (C)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Geometric Mean	107	56	78

Extent of Hydrolysis $(\frac{422}{711})$

0.73

* Expressed as percent of administered L-154,628 equivalents (based on dosage form assay values).

(-) Incomplete data

Study #523

Table 523-1

Observed Maximum Serum Concentrations (C_{max}) of L-154,628 and Total Drug, and Times (T_{max}) at Which They Occurred Following Oral Administration of MK-421 Capsules

Subject	L-154,628 C_{max} (ng/ml)	L-154,628 T_{max} (hr)	Total Drug* C_{max} (ng/ml)	Total Drug* T_{max} (hr)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	42.0	4	66.3	1

Table 523-2

AUC_0^∞ (ng·hr/ml) for L-154,628

Extrapolation technique Not used. (Terminal phase AUC not substracted from total AUC)

Subject	L-154,628 5 mg I.V.	MK-421 P.O. 10 mg Capsules
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Mean	794	497

Caps/IV

S.D. (.09)

* Data did not permit calculation of AUC_0^∞

Study #27

Table 27-1

Individual and Mean Concentrations (ng/ml) of L-154,628 in Serum of Subjects Given 10 mg MK-421 P.O. (Treatment B)

			HOURS											
SUB	PER	DOSE	0	0.5	1	2	3	4	6	8	12	24	48	72	AUC
1	1	0													
2	2	0													
3	1	0													
4	2	0													
5	2	0													
6	1	0													
7	2	0													
8	1	0													
9	2	0													
10	2	0													
11	1	0													
12	1	0													
		MEAN=	0.0	0.8	5.5	23.4	34.3	32.4	25.5	18.7	10.2	2.6	1.1	0.7	

Table 27-2

Individual and Mean Concentrations (ng/ml) of Total Drug Expressed as L-154,628 in Serum of Subjects Given 10 mg MK-421 P.O. (Treatment B)

			HOURS											
SUB	PER	DOSE	0	0.5	1	2	3	4	6	8	12	24	48	72	AUC
1	1	0													
2	2	0													
3	1	0													
4	2	0													
5	2	0													
6	1	0													
7	2	0													
8	1	0													
9	2	0													
10	2	0													
11	1	0													
12	1	0													
		MEAN=	0.0	40.5	61.5	49.1	44.1	39.4	28.5	19.8	10.4	2.6	1.1	0.7	

Table 27-3

Individual and Mean Concentrations (ng/ml) of L-154,628 in Serum of Subjects Given 5 mg L-154,628 I.V. (Treatment A)

			TIME												
SUB	PER	DOSE	0	10'	20'	30'	1H	1.5	2	4	6	8	12	24	48	72	AUC
1	2	1															
2	1	1															
3	2	1															
4	1	1															
5	1	1															
6	2	1															
7	1	1															
8	2	1															
9	1	1															
10	1	1															
11	2	1															
12	2	1															
		MEAN=	0.0	440.3	348.2	300.5	201.8	130.2	91.8	33.1	14.0	7.4	3.2	1.5	0.8	0.6	

study #27

Table 27-4

Observed Maximum Serum Concentrations (C_{max}) of L-154,628 and Total Drug*, and Times (T_{max}) at Which They Occurred Following Oral Administration of MK-421 Tablets

Subject	L-154,628 C_{max} (ng/ml)	L-154,628 T_{max} (hr)	Total Drug C_{max} (ng/ml)	Total Drug T_{max} (hr)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	35.4	4	66.1	1

* L-154,628 plus "MK-421"

Table 27-5

AUC_0^{∞} (ng·hr/ml) for L-154,628

Subject	L-154,628 5 mg I.V.	MK-421 P.O. 10 mg Tablets
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Mean	781	438

study #27

Table 27-6

Urinary Recovery* of L-154,628 Following Administration of L-154,628 I.V. and Recovery of L-154,628 and Total Drug Following Oral Administration of MK-421 Tablets

	A.	B.	C.
Subject	L-154,628 I.V. L-154,628	MK-421 Tablets, P.O. L-154,628	Total Drug
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	95	41	58

* Expressed as percent of administered L-154,628 equivalents (based on dosage form assay values).

(-) "Control" urine had measurable drug.

Table 27-7

Ratios of Urinary Recoveries of L-154,628 and Total Drug for Oral Administration of MK-421 Tablets to L-154,628 for I.V. L-154,628 Administration

* see table above

Subject	L-154,628 (B/A)	Total Drug (C/A)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Geometric Mean	.40	.59

(-) Incomplete Data.

Study # 23

Table 23-1

Urinary Recovery of MK-422 and Total Drug Expressed as Percent of Administered MK-422 Equivalents

Subject	Fasting		Fed	
	MK-422	Total Drug	MK-422	Total Drug
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	31	53	32	58

* Incomplete urine collection.

Table 23-2

Ratio of MK-422/Total Drug for Total Urinary Recoveries

Subject	Fasting	Fed
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Geometric Mean	.56	.54

* Incomplete collection.

Study # 23

Table 23-3

Ratio of MK-422/Total Drug for Fractional Urinary Recoveries to 24 Hours* - Fasting

Subject	0-2 h	2-4 h	4-6 h	6-8 h	8-12 h	12-24 h
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Geometric Mean	.14 (omit #11)	.51	.74	.88	.92	.95

* Less than half the subjects had quantifiable drug concentration in the 24-36 h urine collection and only one had quantifiable concentrations beyond 36 h.

** "Trace" MK-422 only.

NS = no sample (either lost or no void)
NQ = total drug not quantifiable.

Table 23-4

Ratio of MK-422/Total Drug for Fractional Urinary Recoveries to 24 hrs* - Fed

Subject	0-2 h	2-4 h	4-6 h	6-8 h	8-12 h	12-24 h
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Geometric Mean	.10 (omit #2)	.47	.76	.86	.91	.96

* Less than half the subjects had quantifiable drug concentrations in the 24-36 h urine collection and only one had quantifiable concentrations beyond 36h.

** No detectable MK-422.

NS = no sample (either lost or no void).

Study #23

Table 23-5

Area Under the MK-422 Serum Curve (ng·hr/ml) From Time Zero to 24 h (AUC_0^{24}) and From Time Zero to Last Observed Serum Concentration (AUC_0^{LSC})

	Fasting			Fed		
Subject	AUC_0^{24}	AUC_0^{LSC}	AUC_0^{24}/AUC_0^{LSC}	AUC_0^{24}	AUC_0^{LSC}	AUC_0^{24}/AUC_0^{LSC}
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	1209	1304	.93	1173	1262	.93

Figure 23-1

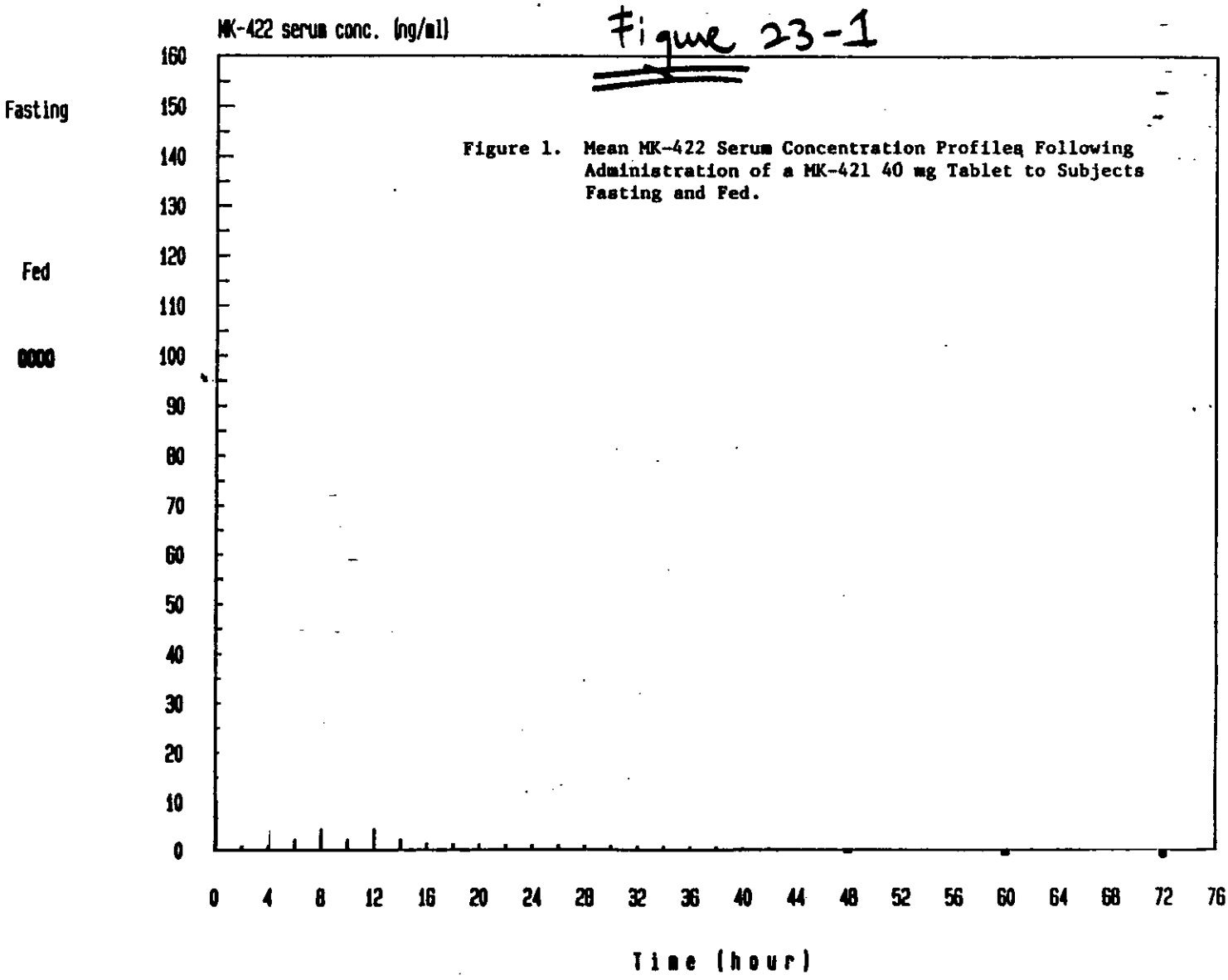


Figure 1. Mean MK-422 Serum Concentration Profiles Following Administration of a MK-421 40 mg Tablet to Subjects Fasting and Fed.

study #17

Table 17-1

Table 1. Standard Curve for Hydrochlorothiazide Plasma Assay.

conc. (ng/ml)	PHR	
0	0	
19.35	0.07	$y = 0.0032x - 0.0093$
38.70	0.12	$r^2 = 0.9986$
96.75	0.25	
193.50	0.64	
290.25	0.91	
387.0	1.22	
580.5	1.86	

Table 17-2

Table 2. Standard Curve for Hydrochlorothiazide Urine Assay

conc (µg/ml)	PHR	
0	0	
1.92	0.07	$y = 0.0404x + 0.0017$
3.84	0.14	
9.60	0.37	$r^2 = 0.9993$
19.20	0.80	
28.20	1.20	
38.40	1.53	
76.80	3.09	

Table 17-3

Table 3. Data for plasma replicate samples assayed on one day.

	Lo-1	Hi-1
	Lo-2	Hi-2
	Lo-3	Hi-3
	LO-4	Hi-4
	Lo-5	Hi-5
	Lo-6	Hi-6
Mean ± SD	79.25 ± 5.83 (ng/ml)	298.58 ± 19.09 (ng/ml)
CV%	7.4%	6.4%
Actual Conc.	77.40 (ng/ml)	290.25 (ng/ml)

Table 17-4

Table 4. Data for urine replicate samples assayed on one day.

	Lo-1	Hi-1
	Lo-2	Hi-2
	Lo-3	Hi-3
	Lo-4	Hi-4
	Lo-5	Hi-5
	Lo-6	Hi-6
Mean ± SD	5.46 ± 0.11 (µg/ml)	29.90 ± 0.7 (µg/ml)
CV%	2.0%	2.3%
Actual Conc.	5.76 (µg/ml)	28.80 (µg/ml)

Study #17

Table 17-5

[redacted]. Data for HCTZ plasma control standard.

Date assayed	control standard (ng/ml)
11/3/81	156.36
11/5/81	184.35
11/11/81	188.80
11/12/81	176.29
11/16/81	189.50
11/18/81	217.72
11/20/81	154.17
11/27/81	191.64
12/2/81	165.97
12/10/81	205.61
12/14/81	190.34
12/15/81	189.69
12/16/81	154.04
12/17/81	154.07
12/21/81	150.64
12/24/81	162.54
12/28/81	172.35
12/29/81	166.06
1/3/82	164.67
1/5/82	161.79
1/7/82	171.81
1/8/82	158.16
1/21/82	177.53
1/23/82	163.14
1/28/82	191.17
1/29/82	183.26
1/30/82	160.38
1/31/82	169.31
2/3/82	178.02
2/4/82	183.55
2/6/82	180.23
Mean ± SD (ng/ml)	174.62 ± 16.29
CV%	9.3

Table 17-6

[redacted]. Data for HCTZ urine control standard.

Data assayed	control standard (µg/ml)
10/8/81	15.12
10/14/81	12.56
10/15/81	14.43
10/16/81	14.26
10/17/81	15.49
10/21/81	14.09
10/26/81	13.35
10/28/81	12.80
11/5/81	12.97
11/6/81	14.51
11/7/81	13.39
11/21/81	14.10
11/22/81	13.89
11/24/81	14.03
11/25/81	13.73
11/27/81	13.39
11/30/81	13.54
12/3/81	12.84
2/17/82	12.70
2/18/82	12.30
2/20/82	13.62
2/24/82	14.23
4/13/82	12.29
Mean ± SD (µg/ml)	13.64 ± 0.85
CV %	6.3

Study #17

Table 17-7

Observed Maximum Serum and Plasma Concentrations,

C_{max} (ng/ml) for MK-422 and HCTZ and the

Times, T_{max} (Hours), At Which They Were Observed

	Treatment											
	A_4		B_{11}		C_4				B_4		A_{11}	
	MK-422		MK-422		MK-422		HCTZ		HCTZ		HCTZ	
Subject	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}	C_{max}	T_{max}
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12A												
Mean	56.1	4.4	68.2	3.9	56.9	4.2	127.99	2.5	127.98	2.4	129.41	2.2

Table 17-8

Average Steady-State Urinary Recoveries* (% of Dose) for MK-422,
Total Drug (TD) and HCTZ

	Treatment A			Treatment B	Treatment C			
Subject	MK-422	TD	MK-422/TD	HCTZ	MK-422	TD	MK-422/TD	HCTZ
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12A								
Mean	35	49	.70**	55	33	48	.68**	52

* Average of recoveries for days 7-10 for MK-422 and TD, and days 6-10 for HCTZ.
** Geometric Mean

Study #17

Table 17-9

Urinary Recovery* of Total Drug Following B.i.d. Administration of Enalapril maleate 10 mg p.o. for 7 Days Alone (A) and with Hydrochlorothiazide 25 mg p.o. (C)

	A										C									
	Day										Day									
	4		5		6		7		8	9	10		4		5		6	7	8	9	10	
Subj	(0-12)	(12-24)									(0-12)	(12-24)	(0-12)	(12-24)							(0-12)	(12-24)
1																						
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12A																						
M	47		45		45	45	50	45	42		64	44	42		49		46	49	47	42	45	63	44

* Expressed as percent of MK-422 equivalents administered 0-12, 12-24 h (1 dose each) on days 4 and 10, 0-24 h (2 doses each) on days 5, 6, 7, 8, and 9.

Table 17-10

Urinary Recovery* of Hydrochlorothiazide Following B.i.d. Administration of 25 mg p.o. for 7 Days Alone (B) and with Enalapril Maleate 10 mg p.o. (C)

(% of dose)

	B										C									
	Day										Day									
	4		5		6		7		8	9	10		4		5		6	7	8	9	10	
Subj	(0-12)	(12-24)									(0-12)	(12-24)	(0-12)	(12-24)							(0-12)	(12-24)
1																						
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12A																						
M	50		50		48	48	50	53	53		77	52	49		50		50	52	50	48	49	68	44

* 0-12, 12-24 h (1 dose each) on days 4 and 10; 0-24 h (2 doses each) on days 5, 6, 7, 8, and 9.

Study #17

Table 17-[redacted]11

[redacted]

Effect of Multiple Doses of Enalapril Maleate (EM) on a Single Dose of Hydrochlorothiazide (HCTZ) as Evaluated By Urinary Recovery of HCTZ (% of Dose)

Subject	Steady-State Urinary Recoveries[a]	Urinary Recoveries Treatment A, Day 11[b]
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12A		
Mean	55	50

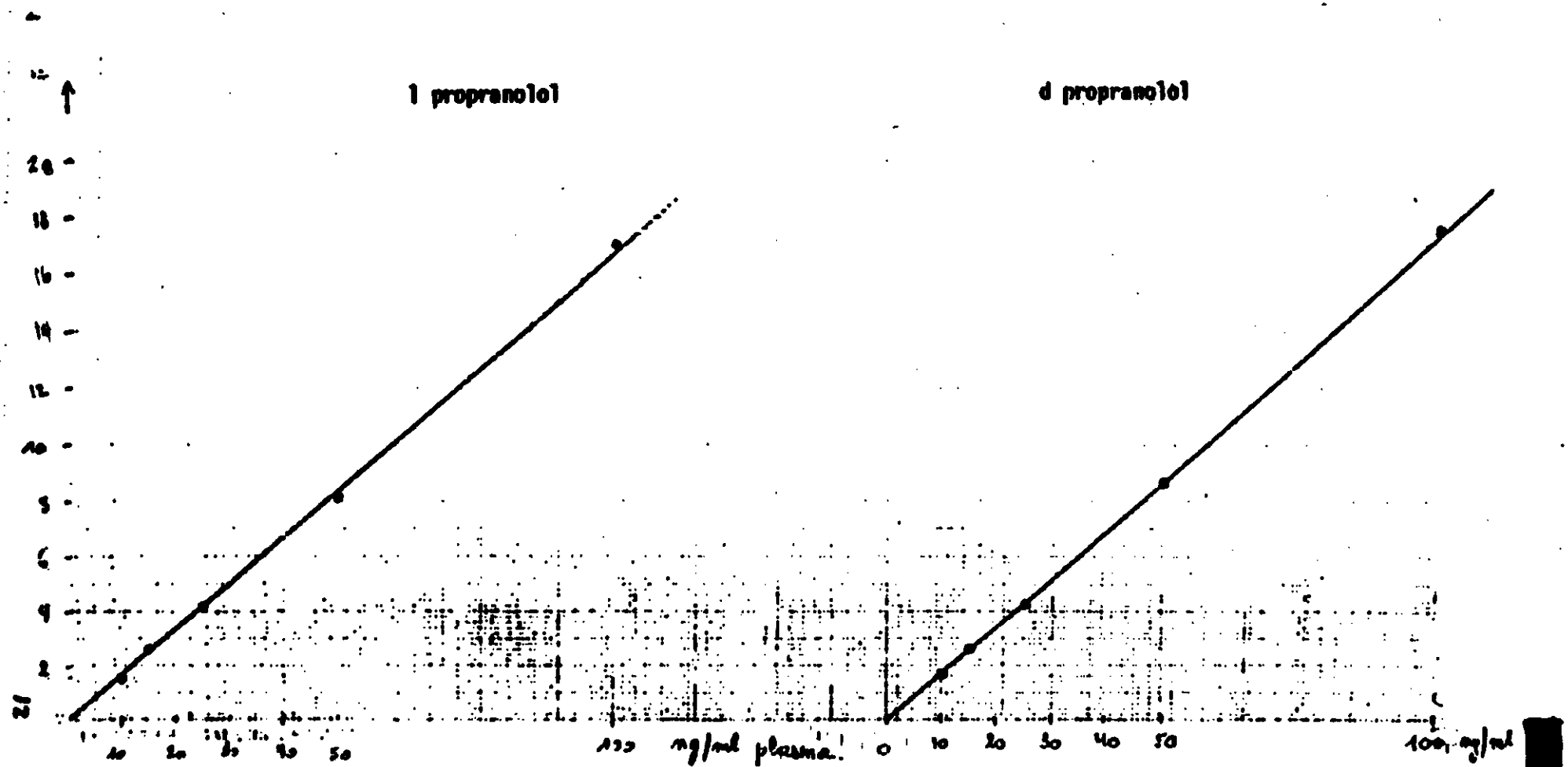
[a] Equivalent to total recovery for a single dose
[b] Total recovery for a single dose of HCTZ administered with a single dose of EM following multiple does of EM.

Study *570

Figure 570-1

[redacted]

(0±S*)



Study # 570

Table 570-1

[redacted]. Standard curves

	1	d
Control	0 cm	0 cm
10 ng/ml	1,5 cm	1,7 cm
15 ng/ml	2,6 cm	2,6 cm
25 ng/ml	4,2 cm	4,2 cm
50 ng/ml	8,1 cm	8,6 cm
100 ng/ml	17 cm	17,6 cm

Table 570-2

[redacted]. Reproducibility data

10 ng/ml		50 ng/ml	
1	d	1	d
1,4 cm	1,8 cm	8,3 cm	8,8 cm
1,6 cm	1,8 cm	8,3 cm	9,2 cm
1,6 cm	1,9 cm	8,2 cm	9,2 cm
1,5 cm	2,0 cm	8,1 cm	8,6 cm
1,6 cm	1,8 cm	7,7 cm	8,2 cm
1,6 cm	1,8 cm	7,9 cm	9,4 cm
M ± SD 1,55 ± 0,08	1,85 ± 0,08	8,08 _0,24	8,91 ± 0,46

(# 570)

Study #570

Table #570-3

Urinary Recoveries[a] of MK-422 and Total Drug (TD)
Following Oral Administration of Enalapril Maleate (EM)
Alone and With Propranolol (P)

Subject	EM Alone			EM with P			Treatment Ratio[b]	
	MK-422	TD	MK-422/TD	MK-422	TD	MK-422/TD	F'	F
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	36	53	.67[d]	24	36	.66[d]	.70[d]	.69[d]

[a] Expressed as percent of administered MK-422 equivalents.
[b] F' = TD, EMcP/TD, EM Alone; F = MK-422, EMcP/MK-422, EM Alone
[c] Missing Data
[d] Geometric Means

Table #570-4

$AUC_{0-\infty}$ (ng.hr/ml) for d- and l-Propranolol
Following Administration of Propranolol Alone
and With Enalapril Maleate (EM)

Subject	l-Propranolol			d-Propranolol		
	Alone	With EM	F[a]	Alone	With EM	F[a]
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	175.95	196.30	1.11	117.21[c]	125.22[c]	1.09

[a] Ratio of AUC with EM/AUC alone, which provides an estimate of relative bioavailability for the two treatments; mean is geometric.
[b] Insufficient data.
[c] Means for those subjects with data for both treatments.

Study #570

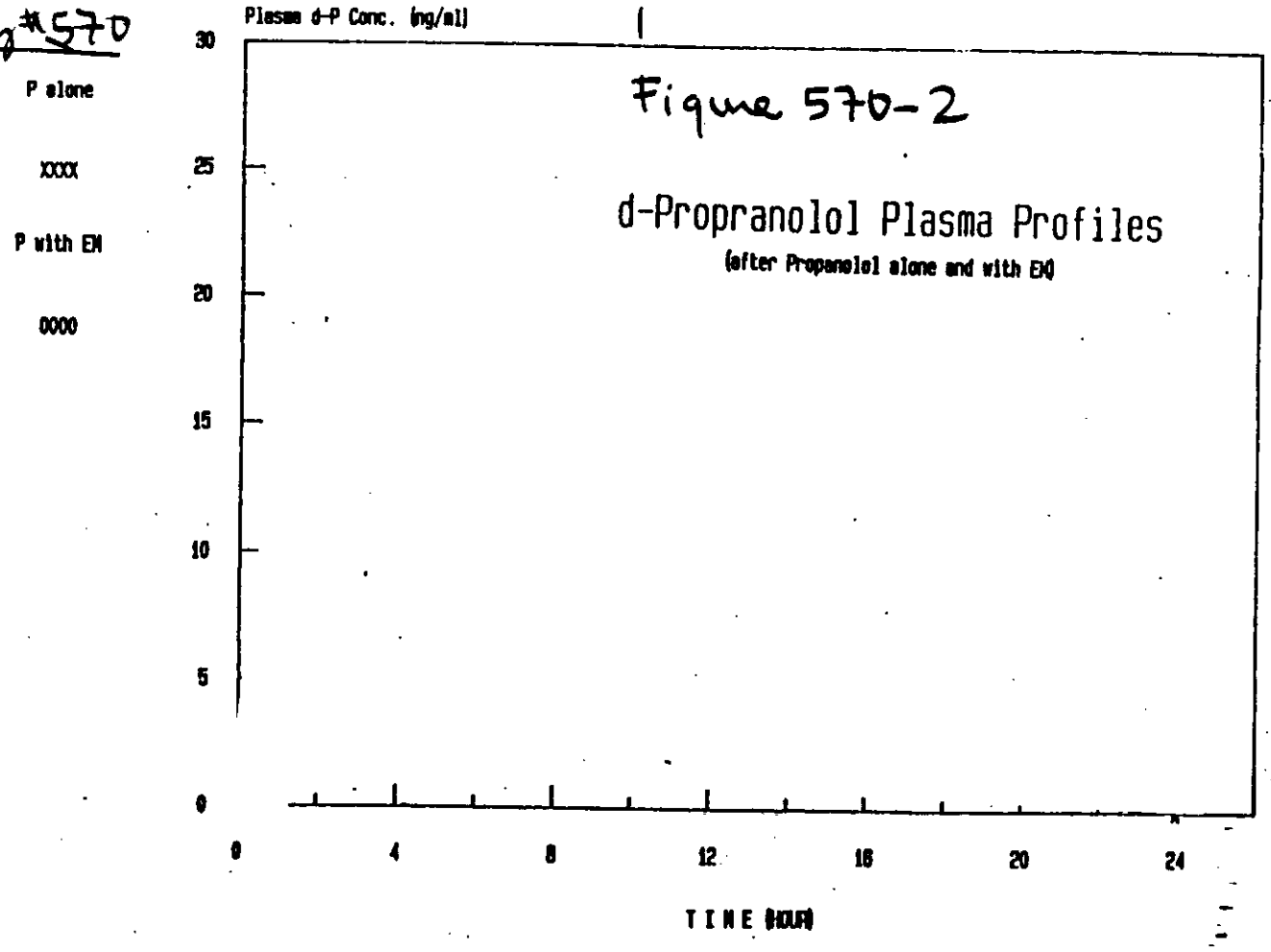


Figure 570-2

d-Propranolol Plasma Profiles

(after Propanolol alone and with EN)

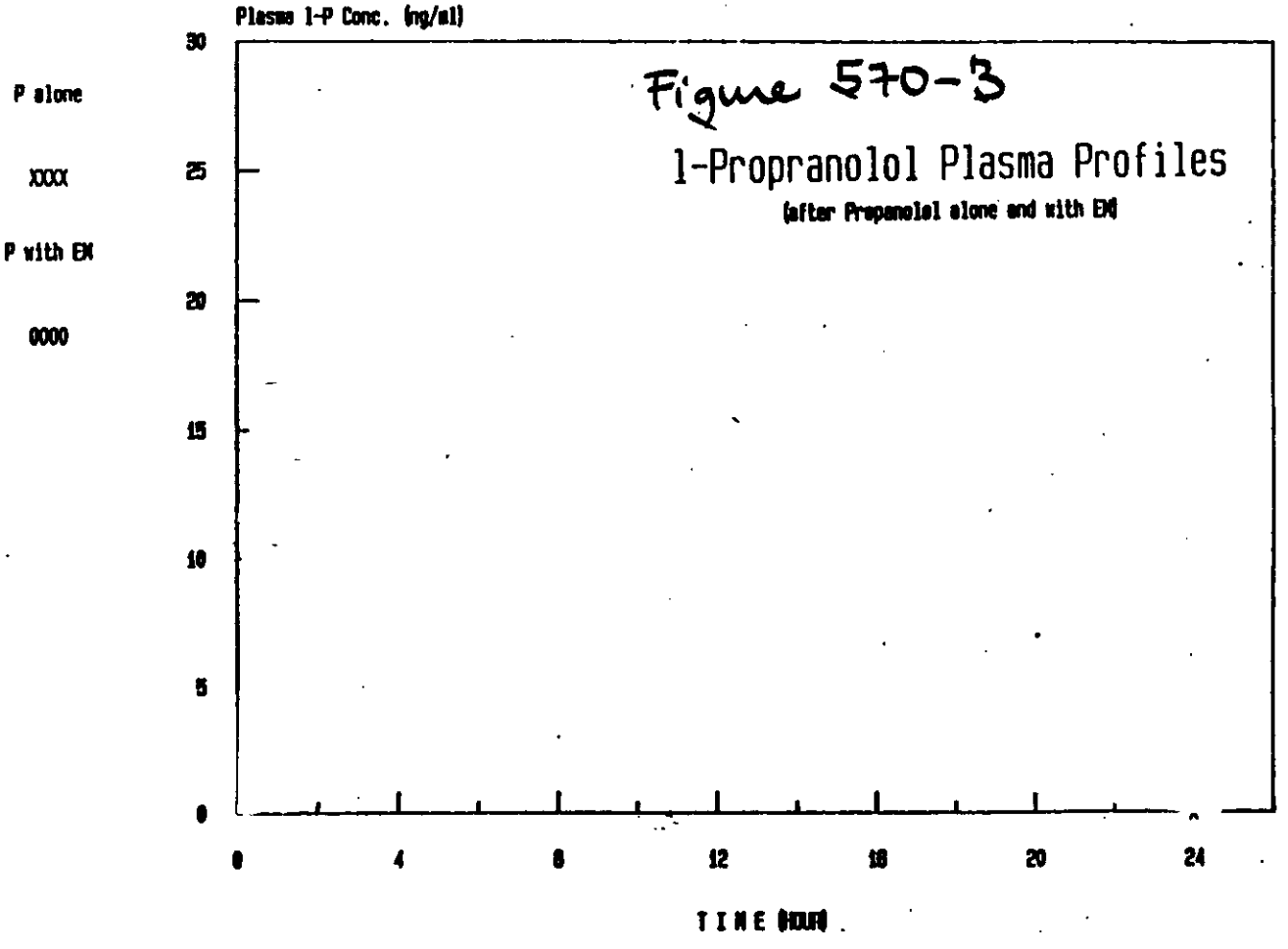


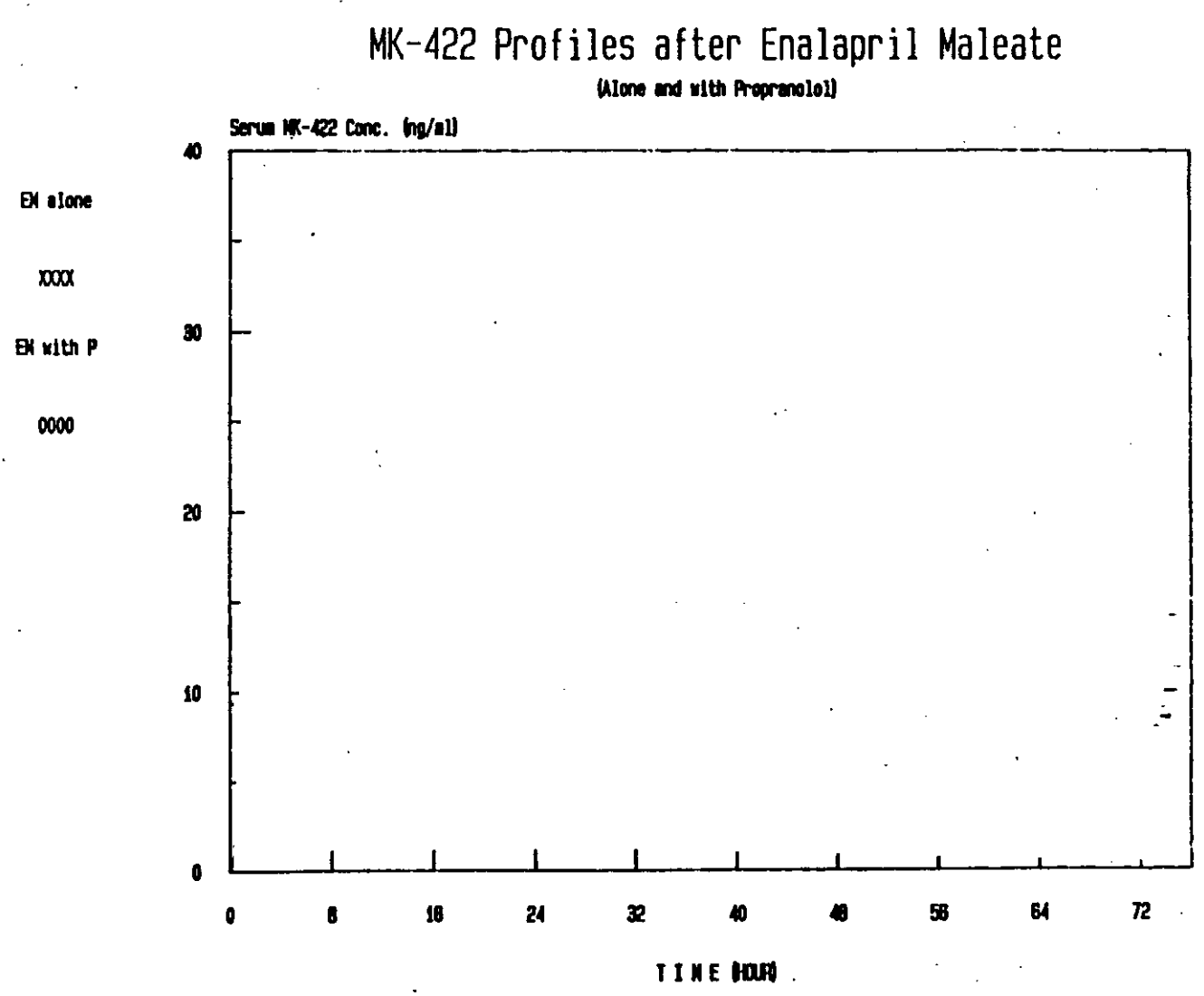
Figure 570-3

l-Propranolol Plasma Profiles

(after Propanolol alone and with EN)

Study #570

Figure 570-4



Study # 634

Table 634-1

[redacted]

Relative Bioavailability* of MK-422 from
Treatment C (Enalapril Maleate plus Digoxin)
Compared to Treatment A (Enalapril Maleate Alone)

Subject	Relative Bioavailability
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Geometric Mean	0.96

* MK-422 urinary recovery ratio, Treatment C/A

Table 634-2

Urinary Recoveries[a] of MK-422 and Total Drug (TD)[b]
Following Oral Administration of Enalapril Maleate
Alone (EM)[c] and with Digoxin (EM + D)[d]

	EM Alone			EM + D		
Subject	MK-422	TD	MK-422/TD	MK-422	TD	MK-422/TD
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	27	42	.64[e]	27	42	.64[e]

[a] Expressed as percent of administration MK-422 equivalents

[b] MK-422 measured after sample hydrolysis, representing MK-422 which was present in the urine as MK-422, itself, plus that which was present as the ethyl ester, enalapril

[c] Treatment A

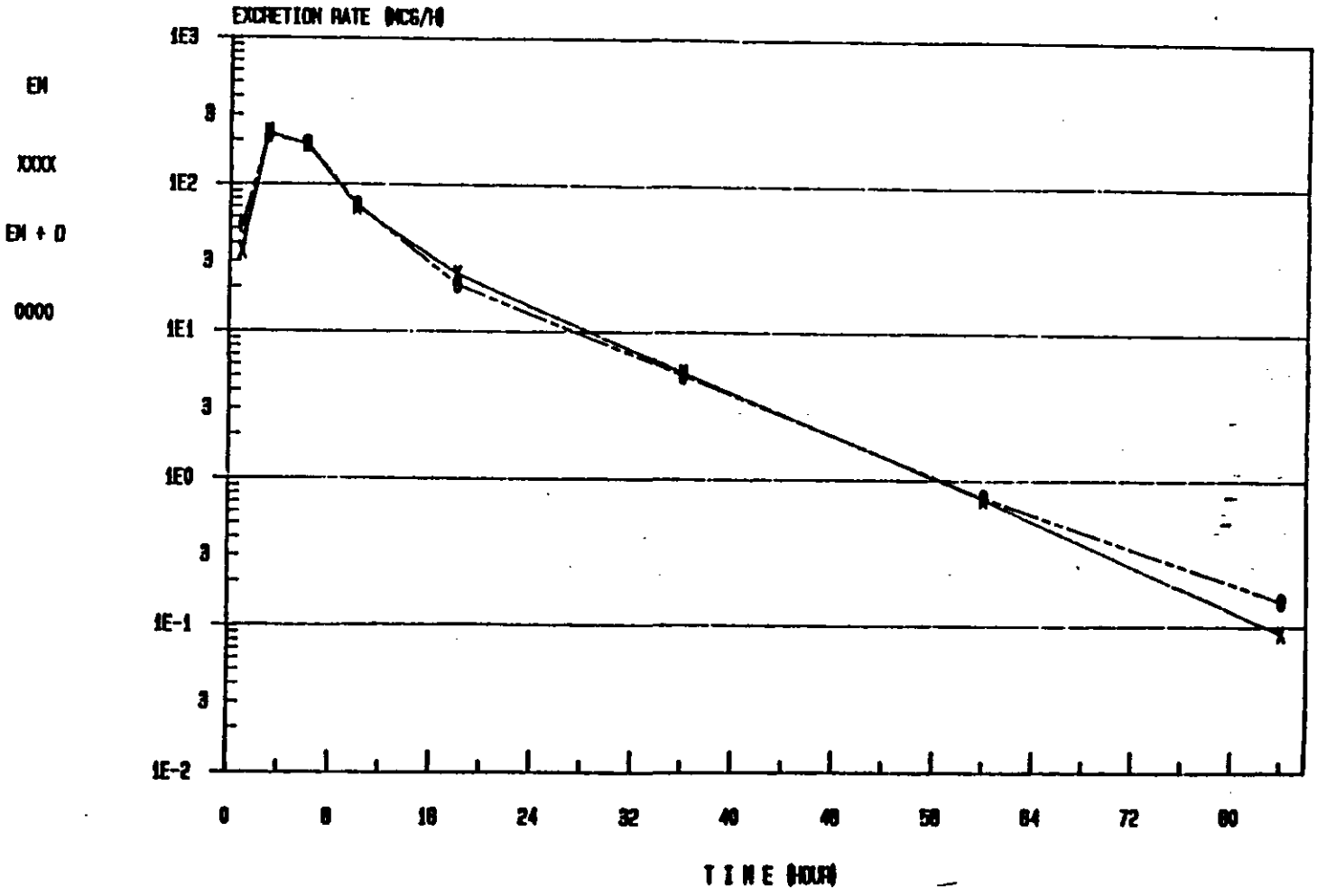
[d] Treatment C

[e] Geometric mean

Study #634

Figure 634-I

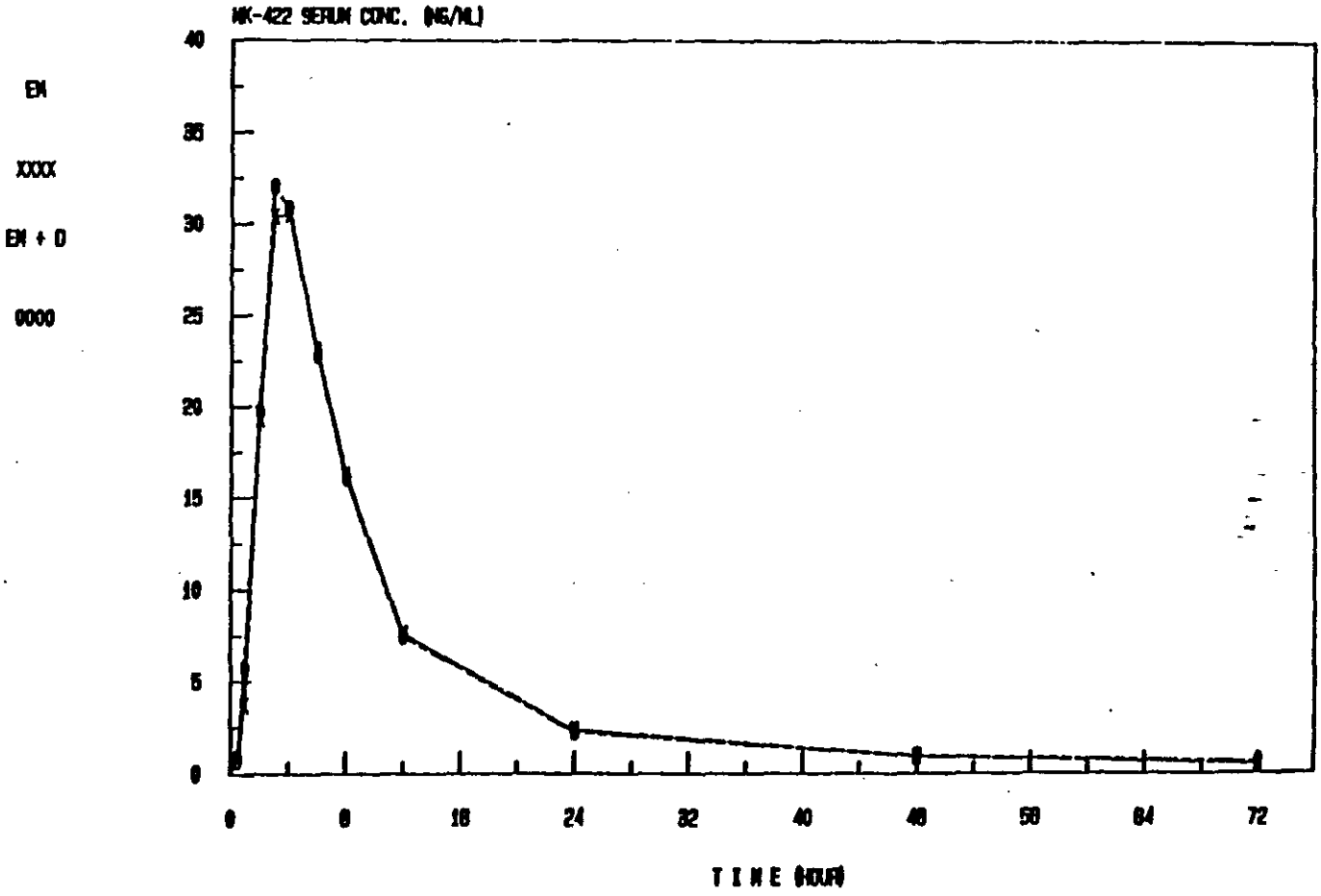
Mean MK-422 Urinary Excretion Rate Plots Following Oral Administration of a Single Enalapril Maleate 10 mg Capsule Alone (EM) and With a 0.25 mg Digoxin Tablet (EM + D).



Study #634

Figure # 634-2

Mean MK-422 Serum Profiles Following Oral Administration of a Single Enalapril Maleate 10 mg Capsule Alone (EM) and With a 0.25 mg Digoxin Tablet (EM + D).



[redacted]

Mean Urinary Excretion Rate Plots for Total Drug (MK-422 Measured After Sample Hydrolysis) Following Oral Administration of a Single Enalapril Maleate 10 mg Capsule Alone (EM) and With a 0.25 mg Digoxin Tablet (EM + D).

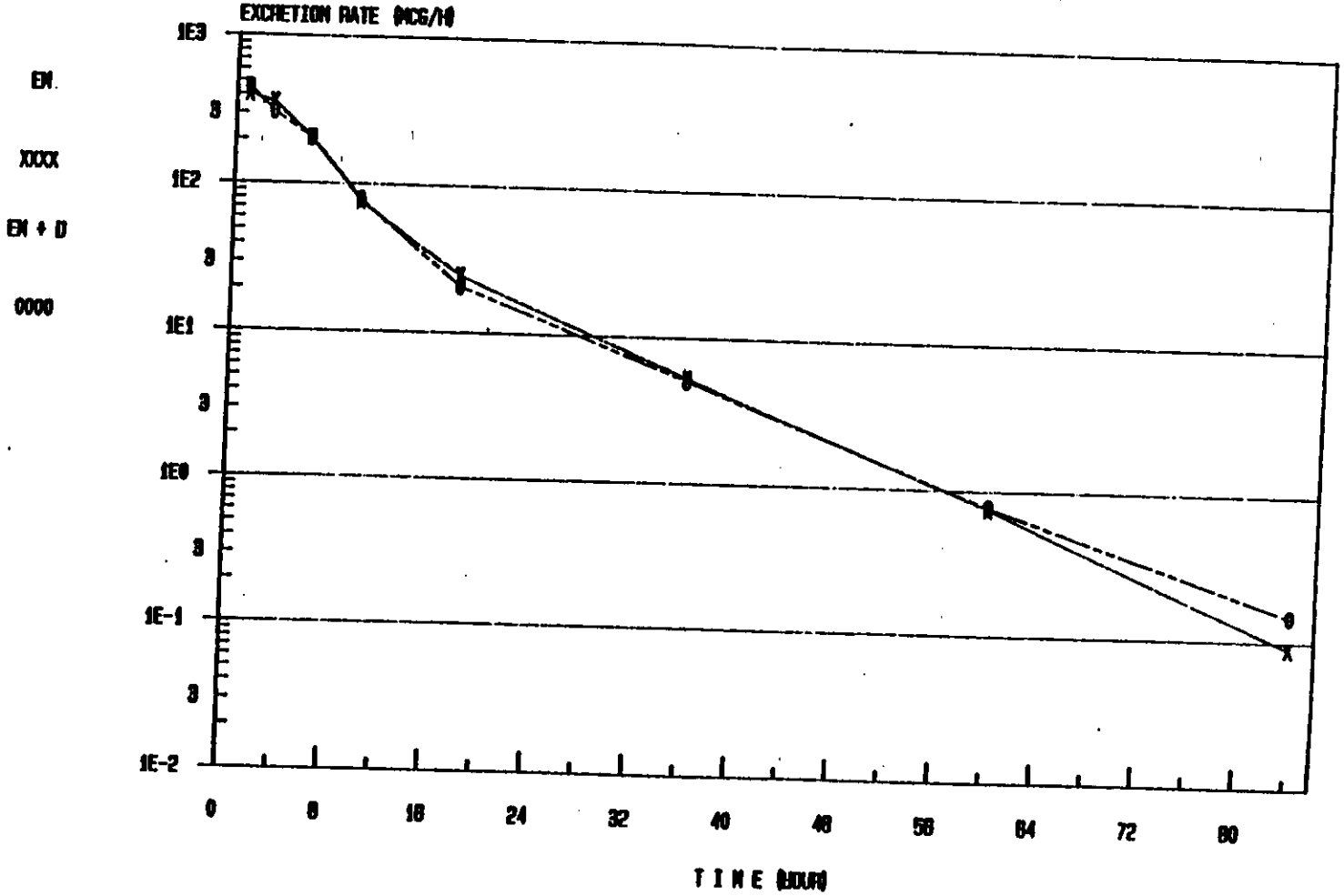


Figure 634-3

Study #634

Figure 618-1

[redacted] - Plasma Furosemide Standard Curve

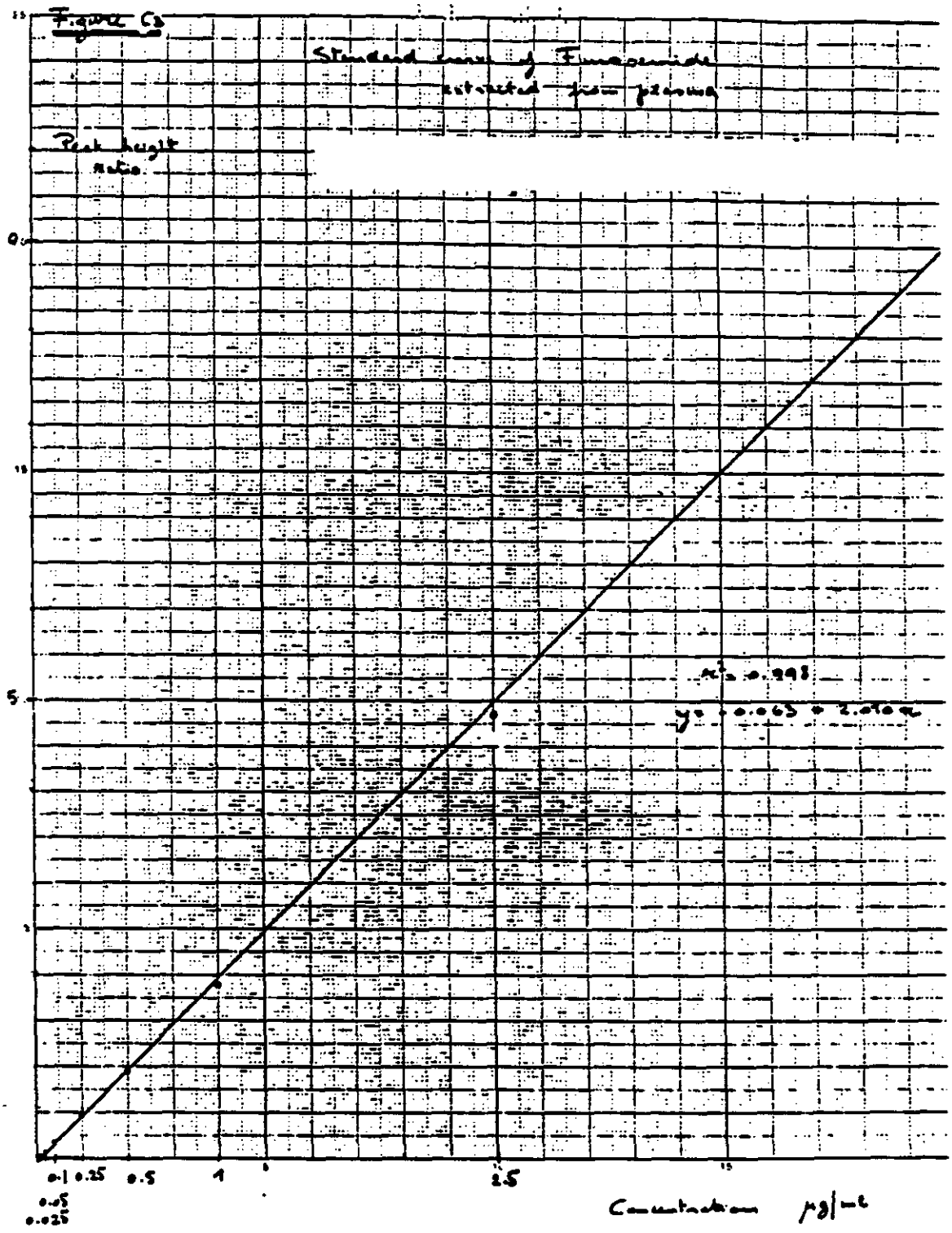


Figure 618-2

[redacted] - Urine Furosemide Standard Curve

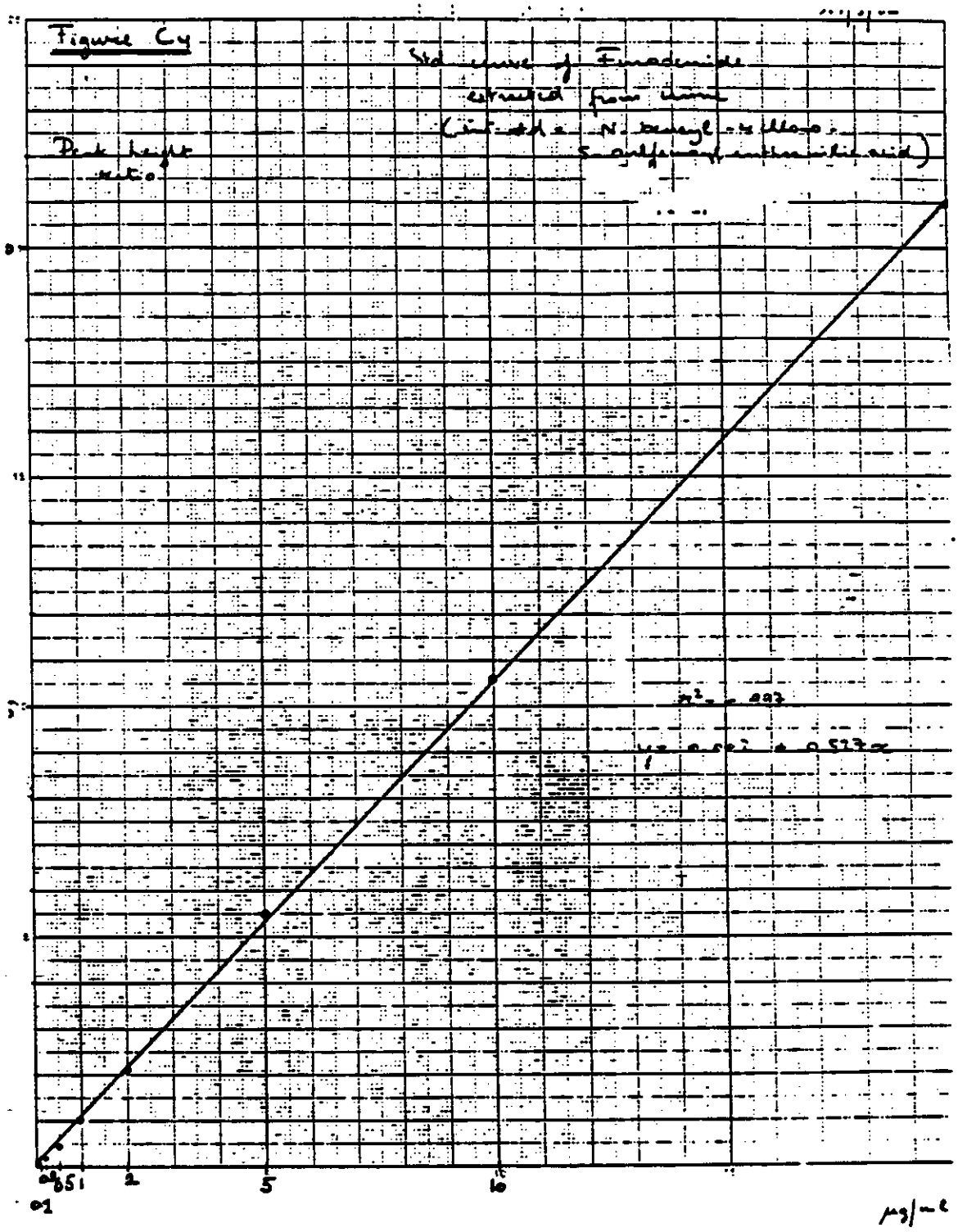


Table 618-1

[redacted]: Reproducibility of the extraction method for Furosemide in plasma and urine.

	Standard Concentration (µg/ml)	Coefficient of Variation (%)
Plasma (n = 6)	0.1	4.0
	0.5	8.0
	2.5	4.5
Urine (n = 6)	0.5	4.8
	2.0	2.4
	10.0	1.5

Table 618-2

[redacted] Furosemide kinetic parameters (mean ± SD) following single oral dose (80 mg) administration to healthy male volunteers in the absence and presence of Enalapril (n = 12).

PARAMETERS	FUROSEMIDE ALONE	FUROSEMIDE WITH ENALAPRIL
Time to Peak Conc. T_{max} (h)	1.50 ± 1.00	1.80 ± 1.00
Peak Plasma Conc. C_{max} (ug/ml)	1.49 ± 0.72	1.33 ± 0.50
AUC_{0-8} (µg/ml.h)	3.33 ± 1.33	3.10 ± 0.97
AUC_{0-12} (µg/ml.h)	3.66 ± 1.37 (n=10)	3.25 ± 0.66 (n=8)
Cumulative Urinary Excretion (mg) (0-96 h)		
Unchanged Furosemide	29.13 ± 6.88	28.13 ± 5.81
Furosemide Glucuronide	6.36 ± 1.39	6.26 ± 1.53
Total Furosemide	35.50 ± 7.68	34.39 ± 6.60
Cumulative Urinary Excretion (% of dose) (0-96 h)		
Unchanged Furosemide	36.42 ± 8.60	35.17 ± 7.27
Furosemide Glucuronide	7.95 ± 1.74	7.83 ± 1.91
Total Furosemide	44.37 ± 9.60	42.99 ± 8.24

Table 618-3

[redacted]

$AUC_{0-12\ h}$ (µg·h/ml) for Furosemide Following Oral Administration of Furosemide Alone (2x40 mg Tablets) and With a 10 mg Enalapril Maleate Capsule

Subject	Furosemide*	Furosemide plus Enalapril Maleate**	Treatment C / Treatment B
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	3.58	3.30	0.94***

* Treatment B
** Treatment C
*** Geometric Mean

Table 618-4

Seventy-two Hour Urinary Recoveries of Furosemide (F) and Furosemide Plus Glucuronide (F_T) Expressed as Percent of Administered Furosemide Following Oral Administration of Furosemide Alone and With Enalapril Maleate

Subject	Furosemide* F	Furosemide* F_T	Furosemide plus Enalapril Maleate** F	Furosemide plus Enalapril Maleate** F_T
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				51
Mean***	36	44	34	42

* Treatment B
** Treatment C
*** Subject 3 excluded from mean due to doubt concerning 2-4h urine collection, Treatment C

Study #618

Table 618-5

Enalapril Maleate & Furosemide
M.A. #618, D.M. #422

[redacted]

[redacted]

Seventy-two Hour Urinary Recoveries of MK-422 and MK-422 plus Enalapril (Total Drug), Expressed as Percent of MK-422 Equivalents Administered, Following Oral Administration of Enalapril Maleate Alone (10 mg Capsule) and With Furosemide (2x40 mg Tablets)

	Enalapril Maleate*			Enalapril Maleate Plus Furosemide**		
Subject	MK-422	Total Drug	MK-422 / Total Drug	MK-422	Total Drug	MK-422 / Total Drug
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	39	57	.69 (Geometric)	38	56	.68 (Geometric)

* Treatment A
** Treatment C
*** Subject 3 excluded from mean due to doubt concerning 2-4h urine collection, Treatment C

Enalapril Maleate & Furosemide
M.A. #618, D.M. #422 [redacted]

Study #618

[redacted]

Table 618-6

Treatment Ratios for Furosemide
and MK-422 Urinary Recoveries

Subject	Furosemide (Treatment C/B)*	MK-422 (Treatment C/A)*
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Geometric Mean	.97	.97

* Treatment A = Enalapril Maleate Alone
Treatment B = Furosemide Alone
Treatment C = Enalapril Maleate Plus Furosemide
(-) Questionable 2-4h Urine Collection, Treatment C

[redacted] Mean Furosemide Plasma Profiles Following Oral Administration of Furosemide Alone (F) and With Enalapril Maleate (F+EM)

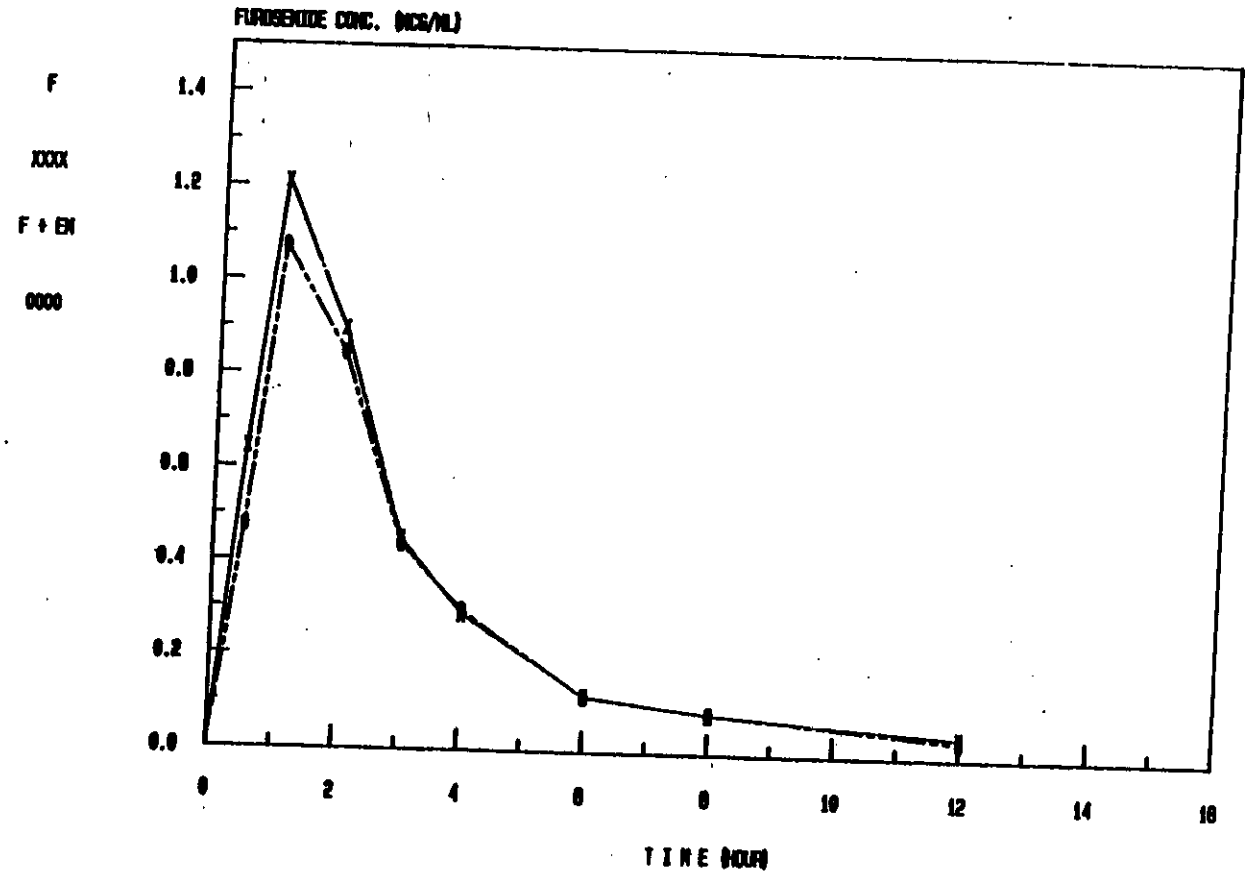


Figure 618-3

Study #618

Study #618

Figure 618-[redacted]4

[redacted] Mean MK-422 Serum Profiles Following Oral Administration of Enalapril Maleate Alone (EM) and With Furosemide (EM+F)