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Editor

Alexander Scriabine, M.D.

Director
Institute for Preclinical Pharmacology
Miles Laboratories, Inc.
New Haven, Connecticut

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Preface

The second volume of *New Drugs Annual: Cardiovascular Drugs* contains thirteen comprehensive reviews on new cardiovascular drugs. Like the first, this volume describes a variety of cardiovascular drugs, including antihypertensives, antiarrhythmics, and antianginals. Some of these drugs have already been approved for clinical use in the United States; others are in clinical evaluation.

Although the editor realizes that most of the cardiovascular drugs have more than one indication, drugs are classified herein by their major clinical use. Ca^{2+} channel antagonists, which are represented in this volume by nitrendipine, diltiazem, bepridil, verapamil, and flunarizine serve as an example of the difficulty of drug classifications. Their classification under various clinical categories is obviously arbitrary and reflects the historical aspects of their development as well as the major promotional emphasis of drug manufacturers.

The discovery of new drugs often precedes the discovery of novel mechanisms of drug action and of therapeutic principles. The drugs are often used as tools for elucidating previously unknown physiological control mechanisms. Discovery of clonidine, for example, led to the elucidation of the presynaptic control of the release of norepinephrine, while the discovery of prazosin facilitated the differentiation between α_1- and α_2-adrenoceptors. Among the drugs discussed in this volume is alinidine, a novel "bradycardic" drug that appears to be useful in the therapy of angina pectoris. Alinidine may become such a tool. It acts directly on the pacemaker cells of the sinoatrial node by a novel but not yet well defined mechanism. Further clarification of its mechanism of action could conceivably improve our understanding of the control of the cardiovascular system.

The comprehensive reviews in this volume contain chemical, pharmacological, pharmacometric, toxicological, and clinical data on new drugs; because of the novelty of these drugs, most of the data cannot be found in textbooks and sometimes not even in professional journals. The advantages as well as the side effects of drugs are discussed in a concise manner. The summaries of toxicological and initial clinical data represent a valuable source of information for scientists, clinical investigators, and research managers in the pharmaceutical industry and in academic institutions.

This and other volumes of the series will be of primary value to preclinical and clinical investigators involved in the development of new drugs; the volumes will also be useful to internists and cardiologists who are interested in new therapeutic approaches.

A. Scriabine

Contributors

Edithe Apoil
Medical Unit
Organon International
Oss, Netherlands

Sherrin Baky
Institute of Clinical Medicine
Syntex Research
Palo Alto, California 94304

E. Bassenge
Lehrstühl für Angewandte Physiologie
Albert-Ludwigs-Universität
7800 Freiburg i.Br., FRG

Alfred F. Fasola
Lilly Research Laboratories
Indianapolis, Indiana 46285

Stephen F. Flaim*
Division of Cardiology
Pennsylvania State University
College of Medicine
Hershey, Pennsylvania 17033

Bernward Garthoff
Bayer AG
Postfach 10 17 09
5600 Wuppertal 1, FRG

Manfred Hanisch
Bayer AG
Postfach 10 17 09
5600 Wuppertal 1, FRG

Stanislav Kazda
Bayer AG
Postfach 10 17 09
5600 Wuppertal 1, FRG

Walter Kobinger
Ernst-Boehringer-Institut für Arzneimittelforschung
A-1121 Wien XII, Austria

Walter R. Kukovetz
Institut für Pharmakodynamik und Toxikologie
Universität Graz
A 8010 Graz, Austria

Jean Claude Lamar
Department of Pharmacology
C.E.R.M.
Riom, France

Christian Lillie
Ernst-Boehringer-Institut für Arzneimittelforschung
A-1121 Wien XII, Austria

Terry D. Lindstrom
Department of Cardiovascular Pharmacology
Lilly Research Laboratories
Indianapolis, Indiana 46285

Richard J. Marshall
Organon Laboratories Ltd.
Newhouse
Lanarkshire ML1 5SH, Scotland

Klaus D. Rämsch
Bayer AG
Postfach 10 17 09
5600 Wuppertal 1, FRG

*Present address: Department of Biological Research, McNeil Pharmaceutical, Spring House, Pennsylvania 19477.

Gerhard Schlüter
Bayer AG
Postfach 10 17 09
5600 Wuppertal 1, FRG

Alexander Scriabine
Miles Institute for Preclinical Pharmacology
P.O. Box 1956
New Haven, Connecticut 06509

Ronald D. Smith
Cardiovascular Pharmacology
Revlon Health Care Group
Tuckahoe, New York 10707

Mitchell I. Steinberg
Lilly Research Laboratories
Indianapolis, Indiana 46285

Kurt Stoepel
Bayer AG
Postfach 10 17 09
5600 Wuppertal 1, FRG

Charles S. Sweet
Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania 19486

Edgar H. Ulm
Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania 19486

Paul M. Vanhoutte
Department of Physiology and Biophysics
Mayo Clinic
Rochester, Minnesota 55905

Jan M. Van Nueten
Department of Pharmacology
Janssen Pharmaceutica
B-2340 Beerse, Belgium

Florence Foster Vickers**
Department of Physiology
Hahnemann University
School of Medicine
Philadelphia, Pennsylvania 19102

Eileen Winslow
Organon Laboratories, Ltd.
Newhouse
Lanarkshire ML1 5SH, Scotland

Peter S. Wolf
Pharmacology Department
Revlon Health Care Group
Tuckahoe, New York 10707

**Present address: Clinical Research International, Merck Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065.

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Enalapril

Charles S. Sweet and Edgar H. Ulm

Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486

In the past few years, several inhibitors of the angiotensin-converting enzyme (ACE) (EC 3.4.15.1) have been developed (32,33,41–43,46). These agents inhibit the conversion of angiotensin I to angiotensin II and prevent, in part, the degradation of the vasodilator bradykinin (39). Throughout this chapter, the term ACE inhibitor (as opposed to an inhibitor of kininase II) is used when referring to the pharmacological action of enalapril and captopril, because most evidence suggests that these compounds act by inhibiting the formation of angiotensin II. Inhibitors of the renin-angiotensin system (RAS), such as ACE inhibitors, have been widely used to characterize the role of the RAS in the control of blood pressure in experimental and clinical situations (5,13,24,37,38,42).

Ondetti and co-workers (32) designed the potent and orally effective captopril. This design was based on the analogy between the catalytic properties of ACE and carboxypepidase A, which had been structurally well defined. Although clinically effective in hypertension, some side effects have been encountered with captopril (5,17–19; see references cited in ref. 27) that are similar to those with D-penicillamine, another agent possessing a free sulfhydryl moiety.

On the assumption that the adverse reactions associated with captopril treatment were attributable to its molecular structure rather than its effect of inhibiting ACE, Patchett and colleagues (33) sought to design potent, specific inhibitors of ACE that lacked a mercapto function and that would be characterized by weak chelating properties. This chapter summarizes the pharmacology, drug metabolism, and early clinical experience of enalapril maleate (MK-421), the prototype drug from this novel series of N-(carboxymethyl)-dipeptides (33). Enalapril is the monoethyl ester of the active ACE inhibitor MK-422 (Fig. 1).

BIOCHEMISTRY OF ENALAPRIL

Enzymatic Studies: Inhibition of Hog Plasma and Purified Rabbit Lung ACE

MK-422 has been characterized as a purely competitive, "tight binding" inhibitor of homogenous rabbit lung ACE (9). The tightness of binding of MK-422 to ACE is primarily a function of a slow off rate from the enzyme, which is about 0.1 that

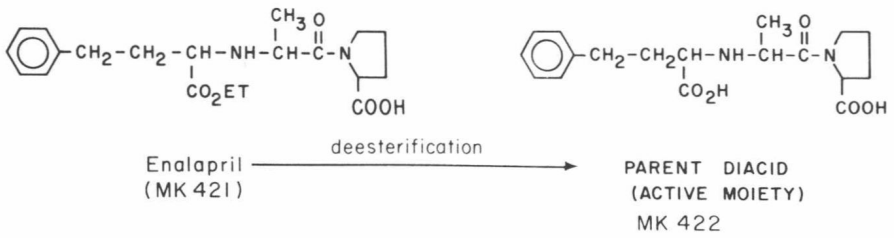

FIG. 1. Structures of enalapril (MK-421) and MK-422 (diacid inhibitor).

TABLE 1. *Comparative* K_i *(rabbit lung ACE) and* I_{50} *determinations (hog plasma ACE) for captopril, MK-422, and enalapril*

Inhibitor	K_I (M)[a]	I_{50}[b]	IC_{50}[c]
MK-422	2.14×10^{-10}	1.2×10^{-9}	1.2×10^{-8}
Captopril	4.98×10^{-10}	2.0×10^{-8}	1.2×10^{-7}
Enalapril	—	1.2×10^{-6}	—

[a]Data from ref. 9.
[b]Data from refs. 22 and 33.
[c]Data from ref. 53 in rat plasma.

of captopril. From both kinetic and binding studies, the K_I for MK-422 has been determined as $2 \pm 1 \times 10^{-10}$ M (Table 1).

IC_{50}s or I_{50}s reported for MK-422 from different laboratories are somewhat higher than the K_I and are not in quantitative agreement (Table 1); this is not surprising, since enzymes from different species and different assay conditions were employed. The studies, however, do indicate that captopril and MK-422 have roughly the same relative potencies (Table 1).

Activation (esterolysis) of enalapril in different ACE-containing tissues, which may be important target organs for angiotensin II, has been evaluated (48,53). Based on the concentrations necessary for a 50% enzyme inhibition, there was a considerable difference in potency of enalapril *in vitro*, depending on the tissue studied; enalapril was highly effective against ACE from plasma and kidney, but not brain and adrenals (53). These differences most likely reflect the relative ability of plasma and tissue esterases to convert enalapril into the active inhibitor MK-422.

When enzyme inhibitors are used as drugs, one concern is that tolerance may develop due to induction of synthesis of the target enzyme. Plasma ACE concentration in rats was shown to increase 2.8-fold after 1 or 2 weeks of treatment with enalapril (15,50); in dogs, there was a 1.5-fold increase (50). Data from human trials (E. H. Ulm, *unpublished*) indicate that the increase in plasma ACE after 1 or 2 weeks of treatment is similar to that found in dogs. Such increases would not be expected to alter the therapeutic effectiveness of ACE inhibitors; in fact, enalapril

has maintained good blood pressure control during subacute or chronic treatment (3,5,14).

Oral Absorption and Metabolism

The inherent chemical stability of enalapril and MK-422 permitted the development of a sensitive radioimmunoassay (RIA) (23) and a converting enzyme inhibition assay (48) for the drug in biological samples. These methodologies supplemented studies that used the radiolabeled drug to determine the disposition and metabolism of enalapril in rats, dogs, monkeys, and man (48,49,52).

Although MK-422 is a potent ACE inhibitor *in vitro* and *in vivo* after intravenous dosing (Table 2), it was poorly absorbed orally both in the animal species tested and in man (48). In dogs and rats, absorption of oral MK-422 at 1 mg/kg was estimated at 12 and 5%, respectively (48). Results of a study using a 10-mg dose of radiolabeled MK-422 given to normal volunteers indicated that absorption based on urinary recovery was about 5% (D. J. Tocco, *personal communication*). Absorption of enalapril in animals and man was clearly superior to that of MK-422 (Table 3), with oral absorption of enalapril in man reported as 61% based on urinary recovery of intact enalapril and MK-422 (49). When a 40-mg dose of enalapril was preceded by a light breakfast, no significant effect of food on absorption was seen (R. K. Ferguson, *personal communication*).

Based on evidence for intact enalapril in serum after oral dosing, bioactivation of enalapril to MK-422 in the dog and man appears to be a postabsorptive process (30,44,45,48,49). In these species, the liver was demonstrated to be capable of carrying out the esterolysis and is presumably the major site of bioactivation (48). The rat, of the species extensively studied, differs from the others in that its plasma contains the requisite esterase(s) (48). Although other rat tissues, besides the liver and plasma, have been implicated as possible sites of bioactivation (53), any plasma contamination of tissue samples could compromise such conclusions. An estimate

TABLE 2. *Comparative intravenous and oral ACE inhibitory activity of enalapril, MK-422, and captopril in rats and dogs*

Species	Agent	Antagonism of angiotensin I pressor responses [ED_{50} μg/kg (±95% confidence interval)]	
		Intravenous route	Oral route
Rats[a]	Enalapril	14.0 (12.2–16.2)	290 (200–420)
	Captopril	26.1 (20.5–33.0)	330 (220–490)
	MK-422	5.1 (4.2–6.2)	2290 (1,540–3,400)
Dog[b]	Enalapril	278 (239–323)	108 (70–170)
	Captopril	80.2 (66.5–97.1)	90 (20–150)
	MK-422	6.4 (4.7–8.0)	172 (96–308)

[a]Data from ref. 44.
[b]Data from ref. 22.

TABLE 3. *Disposition of oral enalapril maleate*

Species	Recovery (0–72 hr) Urine	Feces	Ref.
Man	61 (70)[a]	33 (82)	49
Dog	39 (83)[b]	40	48
Rat	26 (100)	72	48

[a]Percent as MK-422 in parentheses.
[b]0–24 hr urine.

of the minimal extent to which bioactivation occurs in man, based on urinary recovery of MK-422 after oral enalapril, was 43% (49).

No evidence for additional modes of metabolism of enalapril or MK-422 was found in man (49; D. J. Tocco, *unpublished*). Of the species examined, only the rhesus monkey exhibited further metabolism of enalapril. A desprolyl metabolite of MK-422, which accounted for 13% of an oral dose of enalapril, was isolated and characterized from the urine of the rhesus. This metabolite was not detected in the urine of rats, dogs, or man (51; D. J. Tocco, *unpublished*).

Although serum concentrations of MK-422 may not correlate well with antihypertensive effects, good correlations have been seen with inhibition of angiotensin I pressor responses and plasma ACE inhibition (6,40). An inhibition of plasma ACE of more than 80% was required in order to obtain significant inhibition of the angiotensin I pressor response *in vivo* (4). This 80% level of inhibition was found to correspond to an MK-422 concentration in serum of 20 nM (6.6 ng/ml). After a 10-mg dose of enalapril, this level of MK-422 was exceeded for approximately 19 hr (49). Thus the prolonged duration of action of enalapril is supported by the pharmacokinetic data.

Serum concentrations of MK-422 after oral enalapril exhibited polyphasic kinetics (30,49). Due to the exquisite sensitivity of the MK-422 RIA (23), low serum concentrations of inhibitor were measured up to 96 hr after a single dose. This prolonged "terminal" elimination phase apparently does not contribute to a significant accumulation of MK-422 with repeat doses of enalapril (Till et al., *unpublished data*) and probably reflects tight binding to serum ACE. The concentrations of MK-422 measured at these extended time points are of the order of magnitude of plasma ACE concentrations (E. H. Ulm, *unpublished data*).

TOXICITY OF ENALAPRIL

The principal toxicity of enalapril in dogs, when given either alone ($\geq$30 mg/kg/day p.o.) or in combination with hydrochlorothiazide (HCTZ) (3 mg/kg/day plus 10 mg/kg/day enalapril), includes renal functional changes manifested by an increase in serum urea nitrogen, renal tubular degeneration, and death (2). As discussed below, the oral ACE inhibitory activity of enalapril was demonstrated in dogs at

doses of 0.05 to 1.0 mg/kg p.o., which was well below toxic doses. It was also found that the coadministration of enalapril and physiological saline markedly reduced the incidence and extent of renal tubular degeneration in dogs. Although the mechanism for the protective effect of saline is not well understood, it has been observed in our experiments that the antihypertensive effect of enalapril in sodium-deficient rats is attenuated by saline supplementation (42). HCTZ, which potentiates the toxicity of enalapril (2), also enhances its antihypertensive effect (42). It is likely that enalapril, by causing a prolonged reduction in blood pressure, severely disrupts the renal autoregulatory processes and subsequently impairs renal function.

In acute oral toxicity studies, enalapril had an LD_{50} of 2,160 and 1,970 mg/kg in female mice and rats, respectively, and an LD_{50} of 692 mg/kg i.v. for female mice. HCTZ, which enhanced the toxicity of enalapril in rats and dogs on chronic administration, did not alter the acute LD_{50} in mice (W. Bagdon, *personal communication*).

PHARMACOLOGY OF ENALAPRIL

Potentiation of the Contractile Response to Bradykinin *In Vitro*

One property of ACE inhibitors that is frequently used in their characterization is the ability to inhibit bradykinin degradation, which is, in part, an ACE-catalyzed process (39). The potentiation of the guinea pig ileum contractile response to bradykinin by enalapril, MK-422, and captopril has been reported (22). A submaximal concentration of bradykinin, 2.0 nM, was used to determine the concentration of ACE inhibitors required to augment the bradykinin response by 50%. The concentrations of teprotide, captopril, MK-422, and enalapril required to produce an AC_{50} were 1.5, 2.5, 0.07, and 18.0 nM, respectively. The enhancement of bradykinin observed presumably was related to the specific inhibition of ACE, because these agents did not interfere with the musculotropic effects of methacholine. Enalapril was 316 times less potent than MK-422 in the guinea pig ileum, presumably because enalapril was poorly deesterified to MK-422.

In Vivo Potentiation of Bradykinin

The acute vasodilator response to a single dose of bradykinin (intraarterial injection) in the dog hindlimb was readily enhanced by cumulative doses of MK-422. The bradykinin vasodilator response was enhanced 50% at an MK-422 dose of 6.1 (5.8–6.4) μg/kg i.v. (Fig. 2, bottom). In the same experiments, the local vasoconstrictor response to angiotensin I, 0.16 μg/kg i.a., was measured before and after ACE inhibition with MK-422. The dose-response regression line for inhibition of angiotensin I vasoconstrictor responses versus dose revealed that MK-422 had an ED_{50} of 4.4 (4.1–4.8) μg/kg i.v. Thus MK-422 was approximately equiactive with respect to inhibition of angiotensin I and enhancement of bradykinin in the dog extremity.

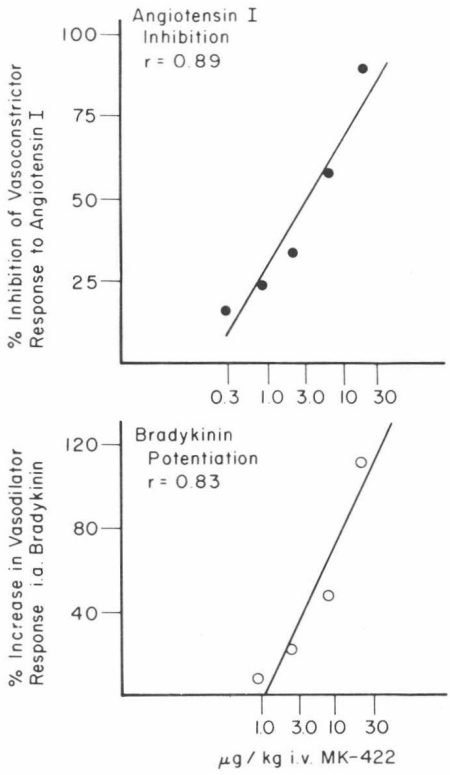

FIG. 2. MK-422-induced inhibition of angiotensin I vasoconstrictor responses **(top)** and enhancement of the vasodilator response to bradykinin **(bottom)** in the dog hindlimb. Dose-response regression lines obtained following MK-422 administered cumulatively are shown *(abscissa). Ordinate* shows the percent reduction in the vasoconstrictor response to intraarterial angiotensin I, 0.16 μg/kg intraarterially **(top)**, and the percent increase in the vasodilator response to bradykinin **(bottom)**.

In Vivo ACE Inhibition: Blockade of Pressor Response to Angiotensin I in Anesthetized Rats and Dogs

At doses lower than that of captopril, MK-422 selectively inhibited the pressor effects of angiotensin I in rats (Table 2). In anesthetized rats, the ED_{50} varied slightly from 5.1 μg/kg i.v. (44) to 8.2 μg/kg i.v. (22). Likewise captopril, for reasons not yet understood, had an ED_{50} that varied from 26.1 μg/kg i.v. (44) to as much as 60.5 μg/kg i.v. (22). Thus MK-422 was about three to 10 times more potent than captopril by the intravenous route.

In anesthetized dogs, MK-422 was also a highly potent inhibitor of the angiotensin I pressor response (Table 2). Intravenous enalapril, however, was approximately 20 times less potent in dogs than in rats. This difference in potency between MK-422 and enalapril in rats and dogs may reflect differences in the degree and rapidity with which the rat and dog hydrolyze enalapril to MK-422. Tocco and coworkers (48) have shown that rat plasma rapidly deesterifies enalapril to MK-422, whereas dog plasma lacks this activity.

The prolonged oral ACE inhibitory activity of enalapril, initially described by Gross et al. (22), has been confirmed in other laboratories (12,47,53). Cohen and Kurz (12) reported that angiotensin I pressor responses in free-moving spontane-

ously hypertensive rats (SHR) were blocked equivalently by 1.0 mg/kg enalapril and 10.0 mg/kg p.o. captopril.

Takata and co-workers (47) compared the ability of SA 446, captopril, and enalapril (during the first 3 min after injection) to block angiotensin I in normotensive rats. This study showed that enalapril, at 25 and 80 nmoles/kg, was less potent than the sulfhydryl inhibitors; at higher doses, it was equally active and exhibited a far longer duration of action.

When constructing cumulative dose-response curves to quantify the percent inhibition of angiotensin I versus dose of ACE inhibitor, the interval between doses becomes important for a prodrug like enalapril. This is especially important in anesthetized dogs (44), a species that shows a time-dependent inhibition of angiotensin I pressor responses due to the slower rate of enalapril hydrolysis to MK-422 (48). The fact that enalapril produced a maximum effect 15 min after intravenous injection while MK-422 inhibited ACE within 3 min in rats again points out the importance of the activation process even in a species that hydrolyzes enalapril more efficiently (53). Enalapril administered intravenously to anesthetized dogs in a cumulative fashion is not potent, having an ED_{50} of 278 μg/kg (Table 2) relative to 6.4 for MK-422 (22,44).

The ED_{50} for enalapril might be smaller if intervals between angiotensin I challenges were lengthened to allow for deesterification. As noted above, a fraction of the enalapril dose is excreted intact in the urine and bile, so that the bioavailability of MK-422 from intravenous enalapril would necessarily be reduced.

The oral ACE inhibitory activity of the N-carboxymethyldipeptide series was greatly improved by esterification (33). In rats, the oral/intravenous ratio was 366 for MK-422 and 21 for enalapril. Bioavailability studies in animals (48) and man (4) showed that the ester (i.e., enalapril) clearly was the preferred form.

Enalapril has a long duration of action following oral absorption. This is illustrated in Fig. 3, which shows data related to the percent inhibition of angiotensin

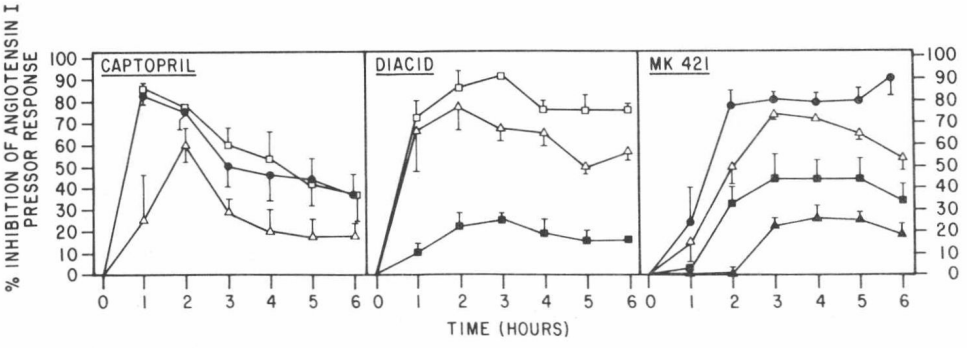

FIG. 3. Oral ACE inhibitory activity of captopril **(left panel)**, MK-422 **(middle panel)**, and enalapril **(right panel)** in unanesthetized dogs. The percent inhibition of the pressor response to angiotensin I, 150 ng/kg i.v. over 6 hr, is shown. Each agent was evaluated in at least three dogs. Open square, 3 mg/kg; solid circle, 1 mg/kg; open triangle, 0.3 mg/kg; solid square, 0.1 mg/kg; solid triangle, 0.05 mg/kg.

I pressor responses in unanesthetized dogs treated with three ACE inhibitors. The onset of action of these agents occurred within 1 hr for captopril and MK-422 (diacid), and at 2 hr with enalapril (MK-421). Examination of these data reveals that the ACE inhibitory activity was declining during hours 2–3 in captopril-treated dogs. In contrast, the peak activity of enalapril and MK-422 was maximal at 2 to 3 hr and persisted essentially unchanged for 6 hr.

The oral ED_{50}s for captopril, MK-422, and enalapril in rats and dogs are summarized in Table 2. The ED_{50} in these experiments was computed from the maximum blockade of angiotensin I in each rat or dog whenever it occurred in the experiment. From these data, it is possible to conclude that in the rat and dog, the oral ACE inhibitory activity of enalapril is similar to that of captopril. The relatively poor oral activity of the parent diacid in rats but not dogs is readily apparent. We have used the same method of computing oral ACE inhibitory activity in SHR (41) and showed that enalapril, with a relative potency of 1.7 (0.7–4.4), was not statistically more potent than captopril. In the study by Cohen and Kurz (12), enalapril at 1.0 mg/kg p.o. and captopril at 10 mg/kg p.o. were approximately equivalent in reducing responses to angiotensin I throughout the first 4 hr, and a partial restoration of pressor responsiveness was observed at the 3- and 4-hr sampling periods. A long duration of action was noted in the study by Takata et al. (47); enalapril, 80 μmoles/kg, blocked angiotensin I 24 hr after a single dose.

MECHANISM OF ANTIHYPERTENSIVE ACTION OF ENALAPRIL

Several investigators have used blockade of the RAS, especially ACE inhibitors and angiotensin II antagonists, to evaluate the role of the RAS in different forms of experimental hypertension (39). Enalapril has been useful in this regard. It has been most potent in those models in which the RAS plays a dominant role, such as salt restriction in normotensive rats and two-kidney renal hypertension. Table 4 summarizes some of the antihypertensive responses of enalapril after acute or subacute treatment. That enalapril falls into the category of a relatively modest antihypertensive, with a reasonably long duration of action, can be appreciated from the data presented in Table 4. In longer term studies (36–38), it is apparent that tolerance to the antihypertensive effect did not develop on repeated administration.

Most investigators find that in SHR, enalapril (1–10 mg/kg p.o.) satisfactorily lowers blood pressure; doses of 15 and 30 mg/kg were found to reduce blood pressure to normotensive levels (37,38). It is also apparent from examining these data, in terms of the dose needed to lower blood pressure, that renal hypertensive rats are not as responsive (7,42), and that DOCA rats (low renin) are totally insensitive (38). We have reported that unless they are rendered renin-dependent with diuretics (42), the low renin perinephritic one-kidney hypertensive dogs are also insensitive to enalapril.

There is a relationship between the antihypertensive response to enalapril and the initial plasma renin activity (PRA) (7,42). These studies showed that enalapril

TABLE 4. *Comparative antihypertensive activity of enalapril in experimental hypertension*

Model/species	Dose (mg/kg p.o.)	Duration of treatment	Maximum anti-hypertensive response (mm Hg range)	Duration of effect (hr)	Refs.
Salt restriction/rat	1–10	acute[a]	19–40	27	42
Two-kidney Grollman/rat	1–10	acute	11–31	7	
One-kidney Grollman/rat	3–30	acute	22–37	24	
SHR	0.3–3.0	acute	14–20	4–8	
SHR treated with HCTZ	3.0	3 days	40	8	
Prevention of SHR hypertension	25	4–15 wk	prevented development of genetic hypertension	persisted for up to 10 weeks after discontinuation	36
SHR	0.1 mg/kg i.v.	acute	21		34
SHR	15 (in drinking water)	6 wk	normotensive levels		37,38
DOCA	30	6 wk	slight increase		
SHR	1.0	acute	15	24	12
SHR	0.1–3.0	acute	20–50	4–6	41
Two-kidney Goldblatt/rat	10	acute	43	24	7
Sodium-restricted sheep	10–50 μg/kg/hr	7-day i.v. infusion	26	7 days	31

[a]Single doses.