Steady-State Pharmacokinetics and Pharmacodynamics of Benazeprilat in Spontaneously Hypertensive Rats (SHR) and Wistar–Kyoto (WKY) Rats

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The effects of the simultaneous steady-state intravenous infusion of benazeprilat, the active metabolite of benazepril HCl, and angiotensin I (AI) on mean arterial blood pressure were investigated in the conscious, unrestrained spontaneously hypertensive rat (SHR) and its normotensive parent strain, the Wistar–Kyoto (WKY) rat. A competitive inhibition model is applied and the limits of its validity are discussed. Deviations from the model are apparent at high drug infusion rates and may relate to the effect of benazeprilat on the clearance of AI. The strains differ in the amounts of angiotensin converting enzyme (ACE) or responsiveness to angiotensin II (AII), the drug clearances, and either the pharmacology or the distribution of the drug. Since the latter two differences are drug dependent, prediction between strains is rendered difficult. This steady-state approach relates the hypertension in the SHR to the amount of ACE or responsiveness to AII and renal function.

KEY WORDS: benazepril; benazeprilat; pharmacokinetics; pharmacodynamics; steady state; i.v. infusion.

INTRODUCTION

Angiotensin converting enzyme (ACE)[3] inhibitors have become a treatment of choice for hypertension (1,2) and congestive heart failure (3,4). The physiology of the angiotensin system is quite complex and may involve changes in mean arterial pressure (MAP) upon long-term treatment with angiotensin I (AI) or ACE inhibitors (5). Benazeprilat (1-carboxymethyl-3S-(1S-carboxy-3-phenyl-propylamino)-2,3,4,5-tetrahydro-1H-[1]-benzazepin-2-one), the active deethoxy diacid metabolite of the new ACE inhibitor, benazepril HCl (6–8), has been used in this study.

In the course of clinical drug development of ACE inhibitors (9), the pharmacological response in healthy volunteers, in particular the MAP, may differ drastically from that seen in patients. AI challenge data from normal subjects are complex and often ignored. A guide for their interpretation could be steady-state PK/PD study in normotensive rats, i.e., Wistar–Kyoto (WKY) rats, and in spontaneously hypertensive rats (SHR). The obtained full dose–response relationship for benazeprilat can serve as a guide for phase I and early phase II studies in man. Similar PK/PD studies in normotensive and hypertensive volunteers could thus yield complete dose–response relationships in fewer patients.

In this paper the PK/PD studies of benazeprilat are reported for WKY rats and SHR.

MATERIALS AND METHODS

Surgical Procedure. Male normotensive Wistar–Kyoto rats (WKY/NCrlBR) and spontaneously hypertensive rats (SHR/NCrlBR) aged 17–19 weeks were obtained from Charles River Breeding Laboratories. Prior to surgery the rats were anesthetized with 1 ml/kg of a 1:10 acepromazine (10 mg/ml):ketamine HCl (100 mg/ml) mixture. The femoral artery and femoral vein were cannulated with polyethylene tubing and the jugular vein was cannulated with silicone rubber tubing (Dow Corning, Midland, MI).

All animals were allowed to recover for at least 5 days prior to experimentation and experiments were performed in conscious, freely moving rats.

Experimental Procedure. Prior to the study, any animal that appeared unhealthy or had lost more than 10% of its initial body weight, or any SHR with a mean arterial blood pressure (MAP) below 150 mm Hg, was omitted from the experiment.

On days 1 and 2 (acclimation days), a blank blood sample (0.2 ml) was collected via the femoral artery cannula, which was subsequently connected to a precalibrated pressure transducer (Gould Inc., Oxnard, CA) to monitor the MAP with the use of a Grass Model D polygraph (Grass Instruments, Quincy, MA). Once baseline MAP was established, the animal received an infusion (Harvard Apparatus) of AI via the jugular vein for an average of 10 min at increasing rates, beginning at 1.4 ng/min and increasing to 3.4, 6.8, 13.6, and 34 ng/min. An infusion of 0.54% saline/0.4% $NaHCO_3$ was started via the femoral vein after the AI infusion on day 2 was completed. This infusion ran overnight and during the AI infusion on day 3. All blood samples were centrifuged immediately after withdrawal, and the plasma samples were frozen at −70°C until assayed.

The third day served as the control for this study, and on each successive day, the infusion rate of benazeprilat through the femoral vein was stepped up from 25 μg/kg/hr (day 4) to 600 μg/kg/hr (day 8). Infusion of benazeprilat was stepped up the previous day after completing the MAP monitoring procedure for that previous day at the appropriate daily infusion rate. Additional AI infusions at the rates of 68 and 136 ng/min were administered on days 4 through 8.

Since the half-life of AI is less than 1 min (10) and that for benazeprilat is approximately 10 min in rats (11), steady-state conditions clearly exist.

Dosing Solutions. Benazeprilat infusion solutions were made up in a 0.54% saline/0.4% sodium bicarbonate solution and filtered through a 0.45-μm membrane (Gelman Acrodisc, Gelman, Ann Arbor, MI). A stock solution of 1 μg/ml angiotensin I (Sigma Chemical Company, St. Louis, MO) was prepared in 0.9% saline containing 0.1% Tween 80 (Sigma Chemical Company).

Data Acquisition. The analog signals corresponding to blood pressure were acquired from the polygraph using a MetraByte Dash-16 analog-to-digital converter at a fre-

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[3] Abbreviations used: AI, angiotensin I; AII, angiotensin II; ACE, angiotensin converting enzyme; MAP, mean arterial blood pressure; SHR, spontaneously hypertensive rat; WKY, Wistar–Kyoto rat.

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quency of 100 points/sec/channel. Raw data were acquired over 1 sec, then integrated to get the mean arterial pressure.

Assay. The plasma samples were analyzed using a commercial radio enzyme assay (Ventrex Laboratories, Portland, ME). This assay is based upon the competitive inhibition of plasma ACE by benazeprilat. For a range of 0–3.0 ng/ml with a limit of quantitation of 0.5 ng/ml, accuracies of 6 and 8% and precisions of 8.5 and 15.2% were determined for plasma from SHR and WKY rats, respectively.

Data Analysis. To analyze the pharmacodynamic data, it is convenient to treat the pressor response and the lowering of the baseline mean arterial pressure (MAP) separately. The pressor response, P, is defined as

$$P(R_I,R_{AI}) = P'(R_I,R_{AI}) - P'(R_I,R_{AI} = 0) \quad (1)$$

where R_I and R_{AI} are the rates of infusion of benazeprilat and AI, respectively, and P' is the MAP for that condition. Such ACE inhibitors are well known to obey a competitive inhibition model (12–14), and P may be related to the rates of infusion by

$$P = \frac{P_{MAX}R_{AI}}{K' + IR_I + R_I} \quad (2)$$

where K', P_{MAX}, and I are adjustable parameters. In the absence of an AI infusion, P_b, the lowering of the baseline MAP may be defined as

$$P_b = P'(R_{AI} = 0,R_I) - P'(R_{AI} = R_I = 0) \quad (3)$$

Within the context of the same competitive inhibition model,

$$P_b = \frac{-DR_I}{E + R_I} \quad (4)$$

where D and E are fitting parameters. Both P and P_b data for individual rats were fit to the competitive inhibition model. Noncompetitive, competitive, and uncompetitive enzyme inhibition models were compared for the data. While all three models have the same degrees of freedom, the competitive inhibition model gave the smallest squared residuals. Further *in vitro* studies of benazeprilat indicated that the competitive inhibition model was appropriate (8).

Table I. Change in Baseline Mean Arterial Blood Pressure[a] in the SHR and WKY Rats Due to Benazeprilat Infusion

Benazeprilat infusion rate (μg/kg/hr)	WKY rats[b]	SHR[c]
25	−6 ± 6	−18 ± 7*
75	−13 ± 5	−21 ± 8
150	−24 ± 3	−28 ± 8
300	−32 ± 10	−36 ± 8
600	−35 ± 9	−45 ± 14
	N = 5	N = 5

[a] Mean ± SD mm Hg.
[b] Actual baseline blood pressure on "control" day, 111.6 ± 14.6 mm Hg.
[c] Actual baseline blood pressure on "control" day, 150.4 ± 8.4 mm Hg.
* $P < 0.05$ between strains (t test).

RESULTS

The baseline blood pressure is defined as the MAP which occurs at a certain drug infusion rate, prior to the infusion of AI. The decreases in the baseline blood pressure, P_b, by benazeprilat in the SHR and WKY rats are summarized in Table I. The effect [see Eq. (3)] of each rate of drug infusion on the baseline MAP is the difference between the baseline MAP at that given drug infusion rate and the baseline MAP obtained on the control day (day 3). The only significant difference in P_b between the two strains was at the drug infusion rate of 25 μg/kg/hr. Unexpectedly, the WKY rats exhibited a similar baseline lowering effect to that of the SHR. There were no significant differences within each strain between the "recovery" and the "control" days.

The pressor response, P, to the AI infusion [see Eq. (1)] was calculated by subtracting the baseline MAP, for that drug infusion rate, from the MAP during the AI infusion, at that same drug infusion rate. The mean pressor responses for each infusion rate and for both strains are summarized in Tables II and III. No significant differences were found between the strains at the higher benazeprilat infusion rates of 150, 300, and 600 μg/kg/hr at any rate of AI infusion. However, at the lower benazeprilat infusion rates there were

Table II. Increase in Mean Arterial Blood Pressure in the WKY Rats in Response to the Administration of Angiotensin I, During the Steady-State Infusion of Benazeprilat[a]

AI rate (ng/min)		Benazeprilat				
	Control[b]	25 μg/kg/hr	75 μg/kg/hr	150 μg/kg/hr	300 μg/kg/hr	600 μg/kg/hr
1.4	3 ± 3*	2 ± 6	5 ± 4*	2 ± 4	2 ± 5	4 ± 4
3.4	10 ± 4*	1 ± 3	3 ± 6	2 ± 4	4 ± 2	3 ± 5
6.8	36 ± 10	6 ± 6	4 ± 6	6 ± 6	5 ± 8	1 ± 7
13.6	51 ± 12*	13 ± 11	10 ± 6	10 ± 8	15 ± 4	12 ± 3
34	52 ± 9**	36 ± 12**	24 ± 9	20 ± 11	22 ± 6	17 ± 6
68		50 ± 18**	41 ± 11	33 ± 12	28 ± 3	27 ± 10
136		59 ± 18**	55 ± 11**	54 ± 18	48 ± 10	44 ± 8
	N = 5	N = 5	N = 5	N = 5	N = 5	N = 5

[a] Mean ± SD mm Hg.
[b] 0.54% NaCl + 0.4% $NaHCO_3$ in water.
* $P < 0.05$ in comparison to the SHR at the same infusion rates (t test).
** $P < 0.01$ in comparison to the SHR at the same infusion rates (t test).

Table III. Increase in Mean Arterial Blood Pressure in the SHR in Response to the Administration of Angiotensin I, During the Steady-State Infusion of Benazeprilat[a]

AI rate (ng/min)	Control[b]	Benazeprilat 25 μg/kg/hr	75 μg/kg/hr	150 μg/kg/hr	300 μg/kg/hr	600 μg/kg/hr
1.4	14 ± 9*	2 ± 3	−1 ± 2*	−3 ± 3	1 ± 3	4 ± 7
3.4	19 ± 8*	3 ± 2	2 ± 4	−3 ± 10	−1 ± 4	2 ± 4
6.8	41 ± 8	5 ± 3	5 ± 8	2 ± 12	2 ± 9	4 ± 8
13.6	76 ± 18*	17 ± 10	11 ± 7	4 ± 6	6 ± 8	7 ± 5
34	91 ± 19**	60 ± 2**	24 ± 8	11 ± 9	19 ± 14	11 ± 5
68		87 ± 8**	52 ± 14	34 ± 6	28 ± 9	30 ± 10
136		105 ± 13**	83 ± 11**	61 ± 11	56 ± 16	49 ± 8
	$N = 5$	$N = 5$	$N = 5$	$N = 5$	$N = 5$	$N = 5$

[a] Mean ± SD mm Hg.
[b] 0.54% NaCl + 0.4% $NaHCO_3$ in water.
* $P < 0.05$ in comparison to WKY rats at the same infusion rates (t test).
** $P < 0.01$ in comparison to WKY rats at the same infusion rates (t test).

some significant differences between the two strains. All of the pressor response values obtained for each AI infusion during the "control" (no drug) period in the SHR were statistically higher than those observed for the same "control" period in the WKY rats. This result is consistent with a higher level of ACE or increased response to AII in the SHR than in the WKY rats.

The individual pressor responses and P_b for each rat of both strains may be fit to a simplified competitive inhibition model [Eqs. (2) and (4), respectively]. Such fits describe the data quite well except at simultaneous high delivery rates of AI and benazeprilat. The fitting parameters for the two strains are listed in Table IV. While P_{MAX} is statistically larger in SHR than WKY rats, a fitting parameter from Eq. (2), I, was statistically larger in WKY rats as compared to SHR.

To interpret the limitations of the competitive inhibition model, the pressor responses predicted from the theoretical curve-fitting were compared with observed responses, for a typical individual spontaneously hypertensive rat (Fig. 1), yielding a correlation coefficient of 0.845. One-third of the predicted pressor responses for this rat deviated from the observations by greater than 10 mm Hg. Of those deviations where the observed response was more than 10 mm Hg greater than the predicted response, all but one measurement reflected benazeprilat drug infusion rates of at least 300 μg/kg/hr. This trend for underestimation at high drug infusion rates was evident in all SHR and WKY rats. Inhibition of ACE by benazeprilat could decrease the clearance of AI and account for these underestimations. For the data shown in Fig. 1, all, except one, of the overestimations that were greater than 10 mm Hg occurred at a drug infusion rate of 75 μg/kg/hr. This deviation in pressor response was not observed in other SHR, although the plasma levels of drug for this rat were consistent with those from the other SHR.

Observed pressor responses for the entire SHR group are compared in Fig. 2 with the estimated pressor responses from the means of the fitting parameters for the individual rats. The agreement was good, except at high drug infusion rates, which gave large deviations from the fit to the competitive inhibition model.

Table IV. Estimated Model Parameters

	WKY rats	SHR
Parameters from fit of P to Eq. (2)		
P_{MAX} (mm Hg)	71 ± 20	146 ± 25
K' (ng/min)	17 ± 7	19 ± 8
I (ng/min) (μg/kg/hr)	0.26 ± 0.11	1.2 ± 0.4
Parameters from fit of P to Eq. (4)		
D (mm Hg)	42 ± 9	45 ± 18
E (μg/kg/hr)	131 ± 63	34 ± 27
From plasma analysis		
CL_I (ml/kg/hr)	1330 ± 180	1960 ± 720

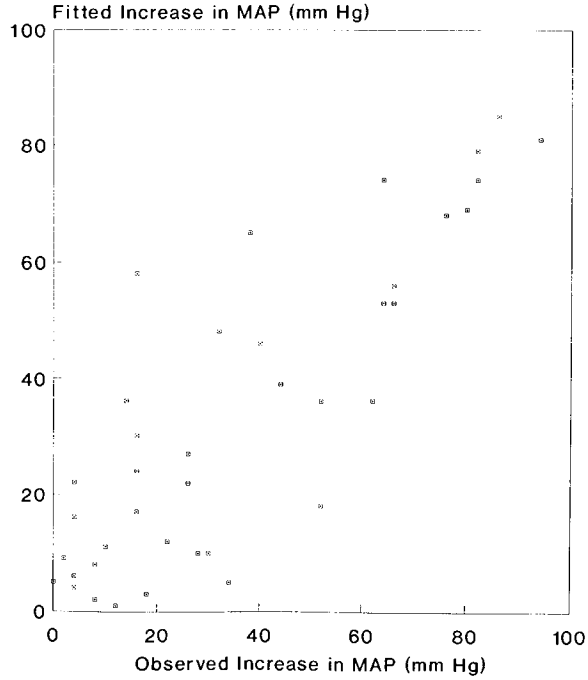

Fig. 1. The fitted vs observed increases in MAP (mm Hg) for a single typical SHR. For this rat $P_{MAX} = 100$, $K' = 12$, and $I = 0.16$.

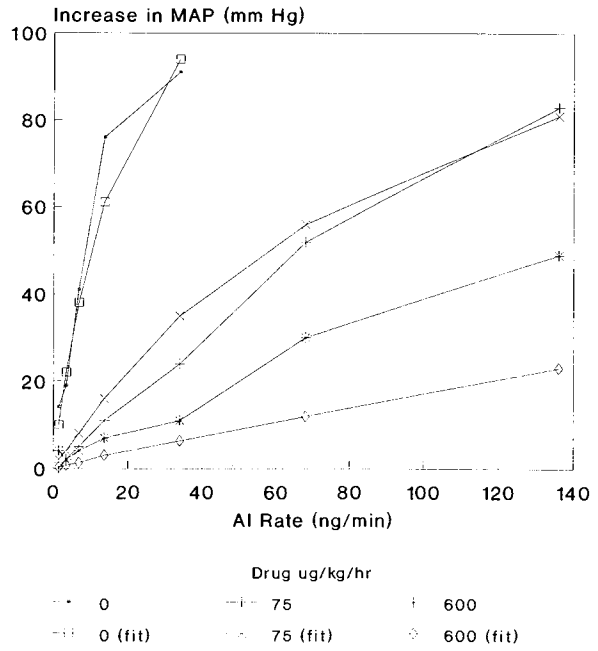

Fig. 2. The mean fitted and observed increases in MAP (mm Hg) in the SHR for different AI and benazeprilat infusion rates. Mean parameters were used for the fitted data.

The mean plasma levels of benazeprilat, C_I, for each drug infusion rate and for both strains are presented in Table V. There is no dose dependence of the clearance in this range of plasma levels, and the intercepts are not statistically different from zero. There is a significant difference in the plasma levels between strains at all drug doses with the exception of the 75-μg/kg/hr infusion rate.

The total clearance was calculated by averaging the clearance for each rat at each drug dose within each strain. The total clearances in the SHR and WKY rats of 1960 ± 716 and 1327 ± 179 ml/kg/hr, respectively, are statistically different ($P < 0.001$, t test).

DISCUSSION

ACE inhibitors are competitive inhibitors *in vitro*, and the mechanism has been confirmed *in vivo* in man and in rats

Table V. Plasma Levels of Benazeprilat[a]

Benazeprilat infusion rate	WKY rats	SHR
25 μg/kg/hr	19 ± 4	14 ± 1*
75 μg/kg/hr	53 ± 4	47 ± 8
150 μg/kg/hr	119 ± 13	77 ± 31*
300 μg/kg/hr	233 ± 30	168 ± 28**
600 μg/kg/hr	467 ± 31	289 ± 69**
Overall clearance (ml/kg/hr)	1327 ± 179	1960 ± 716***

[a] Mean ± SD ng/ml.
* $P < 0.05$ between strains (t test).
** $P < 0.01$ between strains (t test).
*** $P < 0.001$ between strains (t test).

over a limited range of blood pressures in non-steady-state PK/PD studies (12–14). In the present study, the pressor responses for the WKY rats (Table II) and the SHR (Table III) are satisfactorily approximated (within 10 mm Hg for individual rats) by the competitive inhibition model [Eq. (2)] except at high infusion rates of benazeprilat (Figs. 1 and 2). At these high drug infusion rates, the clearance of AI may decrease with increasing plasma concentrations of benazeprilat, and underestimation of pressor responses by this competitive inhibition model might be expected. Plasma levels of AI and AII would be required to account for these deviations quantitatively.

Statistical differences in the pressor responses between the strains occur at high AI infusion rates even in the absence of drug. The SHR is more responsive than the WKY rat to AI (Table III) as reflected by the larger P_{MAX} for the SHR (Table IV). Presumably, this indicates more enzyme binding sites or more ACE present in the SHR. Regulation of sensitivity to angiotensin II (AII) through the number of receptor sites (15–17) could also account for the observed differences between strains. While the fitting parameters, I, for the two strains are statistically different ($P < 0.05$) and larger in the SHR (Table IV), the parameters, K', for WKY rats and SHR are not statistically different.

The baseline lowering of MAP, P_b, by drug infusions is substantial for both WKY rats and SHR. While the maximum P_b for both strains does not differ significantly, the fitting parameter, E, is substantially larger ($P < 0.05$) for WKY rats than SHR. This latter parameter difference is reciprocally related to and consistent with the observed difference in the fitting parameter, I, obtained from the pressor response. However, it is not apparent why the maximum P_b for the two strains should be comparable when the P_{MAX} for the SHR is greater than that for the WKY rat. The baseline lowering and pressor responses are reproducible. The competitive inhibition model is not sufficient to interpret the P_b observations without additional physiological measurements.

The clearances of benazeprilat between strains are statistically different and may be related to differences in renal function. The clearance appears constant over the concentration range studied. Since benazeprilat is thought to be cleared largely by the kidney, the differences in the clearances between the two strains may relate to changes in renal blood flow associated with the pathophysiology of the SHR. Kobrin *et al.* (18) observed that the mean renal blood flows for SHR and WKY rats are 499 ± 43 and 442 ± 33 ml/hr/g kidney, respectively and are statistically different ($P < 0.05$). If we divide the clearances by the renal blood flow for each strain, these ratios are 3.9 ± 1.2 and 3.6 ± 1.2 g kidney/kg for SHR and WKY rats, respectively, supporting the hypothesis that renal function accounts for the differences in clearance. However, biliary elimination of benazeprilat in the rat may indeed be substantial, and the above calculation may be misleading.

While the relationship between pressor response and treatment of hypertension is not clear, prediction of the efficacious drug delivery rate in man is certainly desirable. Some less ambitious correlations are the relationships among pressor response in the two strains and baseline lowering in the SHR. The relationship between WKY rats and

Table VI. Estimated Benazeprilat Infusion Rates

P_b (mm Hg)	P (mm Hg)[a]	Infusion rate (μg/kg/hr) SHR baseline method	SHR pressor response method
−10	35	10	7
−20	25	30	20
−30	15	70	50
−40	10	270	200

[a] Calculated assuming that P = 45 mm Hg is equivalent to P_b = 0 for SHR.

SHR could serve as a guide for predicting effects in hypertensives from normotensive data.

Within the SHR strain, it is assumed that a pressor response of 45 mm Hg (the maximum lowering of P_b) in the absence of drug is equivalent to the untreated hypertensive state in the SHR. By this assumption, the drug infusion rate necessary to lower this pressor response in the SHR may be calculated (pressor response method) and this may be compared with the drug infusion rate necessary to lower P_b in the SHR by the same fixed amount (baseline method). As shown in Table VI, the estimates from these two methods differ by at most 40%, and within the SHR strain, the required estimated rates are reasonably consistent.

The pressor response of the normotensive WKY rats would be a desirable predictor of the pressor response or baseline lowering for SHR. To account for differences between strains, the fitting parameters for WKY rats must be adjusted to those for SHR. P_{MAX} differs for the two strains and should not depend on the drug. However, the parameter, I, also differs substantially and depends on the drug concentration. Adjustment for the parameter, I, would require advance knowledge of the drug effect in the SHR and would make prediction irrelevant.

Finally, the SHR baseline method, when corrected for the clearance of 11.7 L/hr in healthy volunteers (19), predicts a daily dose of 2–6 mg of benazeprilat for control of hypertension in man and this agrees well with the 1–10 mg of benazeprilat, i.e., 2–20 mg of benazepril, studied in hypertensives (20).

Within the context of the competitive inhibition model, hypertension of the SHR appears to be related to differences in renal function, the amount of ACE or responsiveness to AII, and either pharmacological alterations or changes in distribution of the drug. The steady-state competitive inhibition model is a promising approach for the study of hypertension, and the parallelism between WKY rats and SHR appears useful to study in a steady-state paradigm.

REFERENCES

1. H. R. Brunner, H. Gavras, B. Waeber, G. R. Kershaw, G. A. Turini, R. A. Vukovich, D. N. McKinstry, and I. Gavras. Oral angiotensin converting enzyme inhibitor in long-term treatment of hypertensive patients. *Ann. Intern. Med.* **90**:19–23 (1979).
2. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Low-dose captopril for the treatment of mild to moderate hypertension. *Hypertension* **5** (Suppl. 3):139–144 (1983).
3. G. A. Turini, H. R. Brunner, M. Grbic, B. Waeber, and H. Gavras. Improvement of chronic congestive heart failure by oral captopril. *Lancet* **1**:1213–1215 (1979).
4. R. Ader, K. Chatterjee, T. Ports, B. Brundage, B. Hiramotsu, and N. Parley. Immediate and sustained hemodynamic and clinical improvement in chronic heart failure by an oral angiotensin converting enzyme inhibitor. *Circulation* **61**:931–937 (1980).
5. J. H. Laragh. Nephron heterogenicity: Clue to the pathogenesis of essential hypertension and effectiveness of angiotensin-converting enzyme inhibitor treatment. *Am. J. Med.* **87** (6B):2S–14S (1989).
6. U.S. Patent 4473575.
7. J. W. H. Watthey, T. Gavin, and M. Desai. Bicyclic lactam inhibitors of angiotensin converting enzyme. *J. Med. Chem.* **27**:816–818 (1984).
8. J. W. H. Watthey, J. L. Stanton, M. Desai, J. E. Babiarz, and B. M. Finn. Synthesis and biological properties of (carboxyalkyl) amino-substituted bicyclic lactam inhibitors of angiotensin converting enzyme. *J. Med. Chem.* **28**:1511–1516 (1985).
9. G. Waeber, T. Fasanella d'Amore, J. Nussberger, B. Waeber, and H. R. Brunner. Effect of blood pressure and the renin-angiotensin system of repeated doses of the converting enzyme inhibitor CGS 14824A. *Eur. J. Clin. Pharmacol.* **31**:643–646 (1987).
10. W. W. Douglas. Polypeptides-angiotensin, plasma kinins and others. In A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad (eds.), *The Pharmacological Basic of Therapeutics*, 7th ed., Macmillan, New York, 1985, p. 644.
11. CIBA-GEIGY Internal Report B113 (1984).
12. A. Rakhit, G. Kochak, R. Dotson, and V. Tipnis. Disposition of pentopril, a new orally active angiotensin-enzyme inhibitor, and its active metabolite in rats. *J. Pharm. Sci.* **74**:947–952 (1985).
13. A. W. Kelman, J. L. Reid, and J. A. Millar. Concentration effect modelling with converting enzyme inhibitors in man. *Br. J. Clin. Pharmacol.* **15**:506–507 (1983).
14. A. A. Ajayi, N. Hockings, and J. L. Reid. The relationship between serum enalaprilat concentration and the hypotensive effect in man. *Int. J. Clin. Pharm. Res.* **7**:1–3 (1987).
15. B. L. Bean, J. J. Brown, J. Casals-Stenzel, R. Fraser, A. F. Lever, I. A. Millar, J. J. Morton, B. Petch, A. J. G. Riegger, J. I. S. Robertson, and M. Tree. The relation of arterial pressure and plasma angiotensin II concentration: A change produced by prolonged infusion of angiotensin II in the conscious dog. *Circ. Res.* **44**:452–458 (1979).
16. G. Aguilera and K. Catt. Regulation of vascular angiotensin II receptors in the rat during altered sodium intake. *Circ. Res.* **49**:751–758 (1981).
17. B. Folkow. The haemodynamic consequences of adaptive structural changes of the resistance vessels in hypertension. *Clin. Sci.* **41**:1–12 (1971).
18. I. Kobrin, B. L. Pegram, and E. D. Frohlich. Acute pressure increase and intrarenal hemodynamics in conscious WKY and SHR rats. *Am. J. Physiol.* **249**:H1114–H1118 (1985).
19. W. R. Good and A. J. Piraino. Clinical pharmacology and controlled drug delivery. The renin-angiotensin system. *J. Control. Rel.* **11**:315–330 (1990).
20. G. P. Reams, A. Lau, and J. H. Bauer. Effect of benazepril monotherapy in subjects with hypertension associated with renal dysfunction. *J. Clin. Pharmacol.* **29**:609–614 (1989).