

Effects of a Specific and Long-Acting Renin Inhibitor in the Marmoset

JEANETTE M. WOOD, NEELAM GULATI, PETER FORGIARINI,
WALTER FUHRER, AND KARL G. HOFBAUER

SUMMARY Inhibition of renin was induced in conscious marmosets with CGP 29 287, Z-Arg-Arg-Pro-Phe-His-Sta-Ile-His-Lys (Boc)-OMe, a renin inhibitor with a prolonged duration of action. In vitro, CGP 29 287 is a potent inhibitor of primate plasma renin (inhibitory concentration, 50%: human = 1×10^{-9} M; marmoset = 5×10^{-9} M) and less potent against dog (2×10^{-7} M) or rat (3×10^{-5} M) plasma renin. CGP 29 287 is a weak inhibitor of other aspartic proteases such as porcine pepsin or bovine cathepsin D (inhibitory concentration, 50% = 4×10^{-5} M). In furosemide-treated marmosets, CGP 29 287 lowered blood pressure and inhibited plasma renin activity during intravenous infusion and after intravenous bolus injection. The duration of action after intravenous injection was dose dependent and ranged from 1 hour after 0.1 mg/kg to more than 3 hours after 10 mg/kg. High doses of CGP 29 287 (100 mg/kg) were active after oral administration. In all experiments a close relation between inhibition of plasma renin activity and reduction of blood pressure was found. A maximum hypotensive response to CGP 29 287 was associated with complete inhibition of plasma renin activity, and the recovery of blood pressure was accompanied by recovery of plasma renin activity. The hypotensive effects of CGP 29 287 were smaller in untreated than in furosemide-treated marmosets. CGP 29 287 had no influence on blood pressure in marmosets after bilateral nephrectomy or after pretreatment with a converting enzyme inhibitor. CGP 29 287 did not affect the pressor responses to exogenous angiotensin I or angiotensin II. These results indicate that CGP 29 287 is a potent and specific inhibitor of primate renin. In furosemide-treated marmosets CGP 29 287 induced a long-lasting reduction in blood pressure that appears to be entirely due to inhibition of renin. (Hypertension 7: 797-803, 1985)

KEY WORDS • renin activity • furosemide • cathepsin D • pepsin • statine • converting enzyme inhibitor

THE renin-angiotensin system (RAS) plays an important role in blood pressure regulation. This finding has led to considerable interest in compounds that inhibit renin, the enzyme that catalyzes the first step in the formation of the biologically active peptide angiotensin II (ANG II).^{1,2} One of the first described inhibitors of renin was pepstatin, a peptide of fungal origin.³ The poor solubility, low potency, and lack of specificity of pepstatin restricted its experimental application in vivo. Subsequently, analogues of the amino acid sequence around the cleavage site of angiotensinogen were shown to inhibit renin.^{4,5} However, these compounds were of limited usefulness for studies in vivo because of their low potency and short biological half-life. Recently, more potent ana-

logues have been designed by the transition state analogue approach.⁶ This has been achieved by replacing the dipeptide that contains the scissile bond of angiotensinogen with structures that resemble its configuration after activation for cleavage by renin.^{7,8} Potent inhibitors of renin, such as H-77,⁹ H-142,⁷ and statine-containing renin inhibitory peptide (SCRIP),¹⁰ have been developed by this approach. However, all of these inhibitors have a very short biological half-life. They lower blood pressure during intravenous infusion, and blood pressure recovers within minutes after stopping an infusion.⁹⁻¹²

The present study characterizes the in vitro and in vivo properties of CGP 29 287 (Figure 1), a potent and specific renin inhibitor with a prolonged duration of action. CGP 29 287 is an analogue of the amino acid sequence around the cleavage site of human angiotensinogen. It contains statine, the unusual amino acid from pepstatin, as a transition state mimic and has C-terminal and N-terminal protecting groups.

From the Biological Research Department, Pharmaceutical Division, Ciba-Geigy Ltd., Basle, Switzerland.

Address for reprints: Dr. J.M. Wood, c/o Ciba-Geigy Ltd., Klybeckstr. 141, CH4002 Basle, Switzerland.

Received December 13, 1984; accepted April 2, 1985.

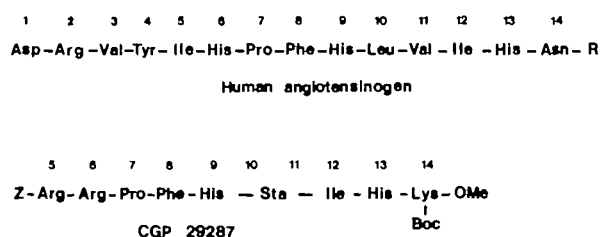


FIGURE 1. Structure of CGP 29 287 in comparison with the N-terminal sequence of human angiotensinogen. Z = benzyl-oxycarbonyl; Boc = t-butyloxycarbonyl; Me = methyl; Sta = statine.

Materials and Methods

In Vitro Evaluation

The inhibitory potency of CGP 29 287 against renin in human, marmoset, dog, and rat plasma was determined. A human plasma pool was collected from male volunteers pretreated with a diuretic. Marmoset, dog, and rat plasma pools were collected from animals maintained on normal diets. Ethylenediaminetetraacetic acid (EDTA) was used as the anticoagulant. Plasma renin activity (PRA) was measured as the rate of angiotensin I (ANG I) formation after incubation (37 °C) of the endogenous renin and angiotensinogen in plasma at pH 7.2. The incubation mixture contained 200 μ l of plasma, 10 μ l of 0.16 M 2,3-dimercaptoethanol, and 100 μ l of buffer (1 M tris(hydroxymethyl)aminomethane (Tris)/acetate, pH 7.2) with or without CGP 29 287 in various concentrations. The ANG I formed after 1 or 2 hours of incubation was measured by radioimmunoassay.¹³ The CGP 29 287 did not cross-react with the antibody to ANG I. Samples were incubated in duplicate and measured in triplicate in the radioimmunoassay. Corrections were made for the ANG I present in plasma before incubation. Percentage inhibition of PRA was calculated by comparing the amount of ANG I produced with and without CGP 29 287. The concentration of CGP 29 287 that inhibited PRA by 50% (IC₅₀) was determined for each species.

The inhibitory potency of CGP 29 287 against two other aspartic proteases, pepsin and cathepsin D, was determined. Porcine pepsin (0.4 μ g/ml; Boehringer, Mannheim, West Germany) or bovine cathepsin D (7.5 μ g/ml; Sigma Chemical Co., St Louis, MO, USA) was incubated at 37 °C for 30 minutes with hemoglobin (2.5 μ g/ml; Merck, Darmstadt, West Germany) as a substrate in the presence and absence of CGP 29 287 in varying concentrations. The buffer was 0.2 M potassium chloride/hydrochloric acid (pH 2.0) for the pepsin assay and 0.1 M citrate/phosphate (pH 3.2) for the cathepsin D assay. After incubation, proteins were precipitated with perchloric acid and the absorbance of the supernatant was measured at a wavelength of 280 nm.

In Vivo Evaluation

Marmosets (*Callithrix jacchus*; Ciba-Geigy, Siseln, Switzerland) of both sexes, weighing between 300 and 400 g, were fed a pellet diet (normal salt; NAFAG, Gossau, Switzerland) supplemented with fruit. One or 2 days before an experiment, with the animals under anesthesia, catheters were implanted in a femoral artery for measurement of blood pressure and in a lateral tail vein for injection or infusion of substances.^{11, 14} During an experiment, marmosets were sedated with diazepam (0.3 mg/kg i.p.) and kept in restraining tubes. Mean blood pressure was recorded continuously, and heart rate was measured at fixed intervals. Except where stated, all marmosets received an injection of furosemide (5 mg/kg i.v.) 30 minutes before the beginning of an experiment to stimulate renin release.

CGP 29 287 is soluble in aqueous solution in concentrations up to 100 mg/ml. For intravenous and oral administration, CGP 29 287 was dissolved in sterile isotonic (0.9%) saline. Solutions were freshly prepared on the day of an experiment.

Blood samples were collected from the arterial catheter into chilled, EDTA-coated tubes (Eppendorf, Hamburg, West Germany). The PRA was measured as described previously after 50 μ l of plasma had been incubated with 10 μ l of 1 M Tris/acetate buffer (pH 7.2) containing 10% vol/vol 0.16 M 2,3-dimercaptoethanol.

Furosemide-Treated Marmosets

CGP 29 287 was infused (40 μ l/min) intravenously in doses of 0.001 ($n = 4$), 0.01 ($n = 5$), or 0.1 ($n = 5$) mg/kg/min over 30 minutes. Isotonic saline was infused (40 μ l/min) for 15 minutes before and 30 minutes after infusion of CGP 29 287. As a control, one group of five marmosets received only saline for the entire infusion period. Blood samples for measurement of PRA were taken immediately before beginning the infusion, after 30 minutes of infusion, and 30 minutes after stopping the infusion.

CGP 29 287 was also administered as an intravenous bolus injection (0.5 ml/kg) in doses of 0.001 ($n = 4$), 0.01 ($n = 6$), 0.1 ($n = 5$), 1 ($n = 7$), or 10 ($n = 4$) mg/kg. As a control, one group of six marmosets received only saline (0.5 ml/kg). Blood samples for measurement of PRA were taken 0, 5, 30, 60, 120, and 180 minutes after injection.

CGP 29 287 was administered by gavage (1 ml/kg) in a dose of 100 mg/kg ($n = 4$). The control group ($n = 4$) received saline (1 ml/kg) only. Blood samples for measurement of PRA were taken 0, 30, 60, 120, and 180 minutes after administration. One group of four furosemide-treated marmosets received the converting enzyme inhibitor teprotide (2 mg/kg i.v.) 30 minutes before CGP 29 287 was infused in a dose of 0.1 mg/kg/min for 30 minutes. The pressor response to ANG I or ANG II (500 ng/kg i.v.) was measured before and during the infusion of CGP 29 287 (0.1 mg/kg/min) in three marmosets. The response was

tested in duplicate, and the mean response before and during infusion of CGP 29 287 was compared.

Untreated and Nephrectomized Marmosets

Saline (40 μ l/min; $n = 6$) or CGP 29 287 (0.1 mg/kg/min; $n = 6$) was infused for 30 minutes in marmosets that were not pretreated with furosemide. Blood samples were taken at the same times as in the infusion experiments already described. CGP 29 287 was administered in doses of 1 and 10 mg/kg i.v. in four marmosets 1 day after bilateral nephrectomy. Blood samples for measurement of PRA were taken before and 1 day after nephrectomy.

Statistics

All values in the text and figures are means $\pm$ SEM. The statistical significance of differences between mean values was calculated by paired Student's *t* test (two-sided).

Results

In Vitro Evaluation

CGP 29 287 inhibited human renin with an IC_{50} of 1×10^{-9} M (Figure 2A). CGP 29 287 was only five-fold less potent against marmoset renin but was 200-fold less potent against dog renin and 30,000-fold less potent against rat renin (see Figure 2A). CGP 29 287 was 40,000-fold less potent against porcine pepsin and bovine cathepsin D than against human renin (Figure 2B).

In Vivo Evaluation

Effects in Furosemide-Treated Marmosets

Infusion of saline had no effect on blood pressure or PRA (Figure 3). Blood pressure was lowered significantly during infusion of all doses of CGP 29 287, and the magnitude of the hypotensive response after 30 minutes of infusion was similar after all doses (see Figure 3). The duration of the hypotensive response was dose dependent (see Figure 3). Blood pressure had recovered by about 60% 30 minutes after stopping the infusion of 0.001 mg/kg/min, whereas the full response persisted for up to 30 minutes after the 0.01 and 0.1 mg/kg/min doses (see Figure 3). The PRA was reduced to unmeasurable levels after 30 minutes of infusion of all the doses of CGP 29 287 (see Figure 3). After stopping the infusions, recovery of PRA was dose dependent and followed a similar time course to the recovery of blood pressure.

Mean absolute values for blood pressure, heart rate, and PRA before, during, and after infusion of the 0.1 mg/kg/min dose are shown in Figure 4. The maximum hypotensive response occurred within 10 minutes after beginning the infusion. There was no significant influence of CGP 29 287 on heart rate.

There was a gradual decrease in blood pressure dur-

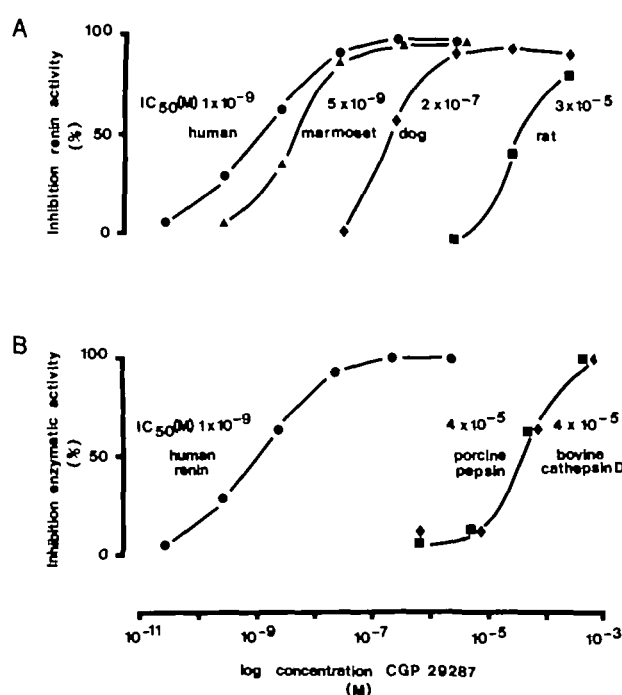


FIGURE 2. A. Species specificity of renin inhibition by CGP 29 287; inhibition of renin in human, marmoset, dog, and rat plasma by CGP 29 287. B. Enzyme specificity of inhibition by CGP 29 287; inhibition of human renin, porcine pepsin, and bovine cathepsin D by CGP 29 287. IC_{50} = inhibitory concentration, 50%.

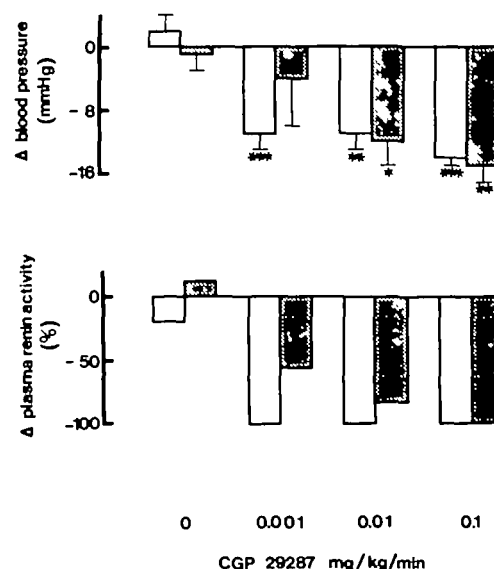


FIGURE 3. Mean changes in blood pressure and plasma renin activity after 30 minutes of intravenous infusion (open columns) or 30 minutes after stopping the infusion (hatched columns) of saline ($n = 5$) or CGP 29 287 in doses of 0.001 ($n = 4$), 0.01 ($n = 5$), or 0.1 ($n = 5$) mg/kg/min. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

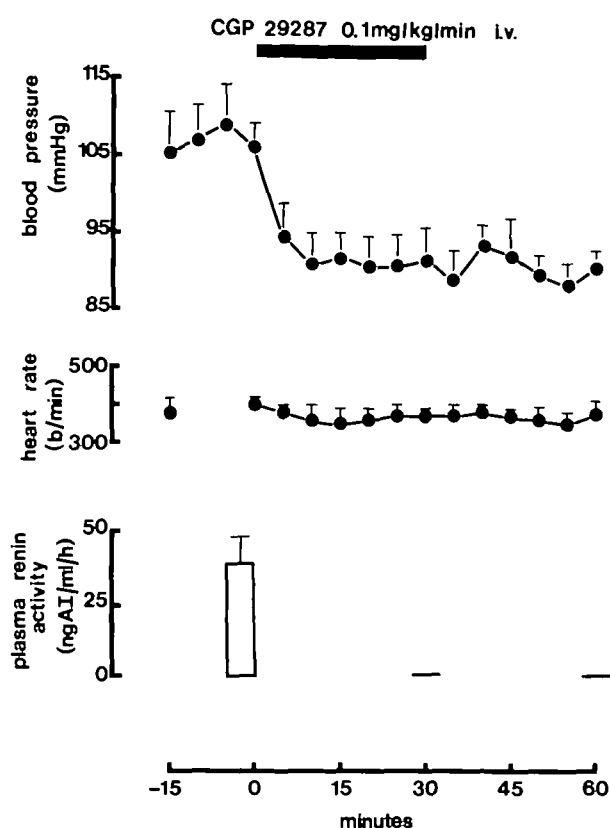


FIGURE 4. Mean arterial blood pressure, heart rate, and plasma renin activity in five furosemide-treated marmosets before, during, and after infusion of CGP 29 287, 0.1 mg/kg/min. AI = angiotensin I.

ing the first hour after injection of saline (Figure 5). The lowest dose of CGP 29 287 (0.001 mg/kg) induced a small but significant fall in blood pressure 10 minutes after injection (see Figure 5). The maximum hypotensive response was observed with doses of 0.1 mg/kg and above. As in the infusion experiments, the duration of the hypotensive response was dose dependent. Blood pressure was similar to the value seen in control marmosets within 30 minutes after the 0.001 mg/kg dose. Increasing doses had a progressively longer duration of action with the full response persisting for more than 3 hours after the 10 mg/kg dose. Injection of saline had no significant effect on PRA (see Figure 5). The PRA was inhibited by 70% 5 minutes after injection of 0.001 mg/kg and by 95% after 0.01 mg/kg. Complete inhibition of PRA was observed 5 minutes after doses of 0.1 mg/kg and above (Figures 5, 6). Recovery of PRA was dose dependent and followed a similar time course to the recovery of blood pressure.

Mean absolute values for blood pressure, heart rate, and PRA after bolus injection of the 0.1 mg/kg dose are shown in Figure 6. The maximum hypotensive response occurred within 10 minutes after injection. Injection of CGP 29 287 had no significant effects on heart rate.

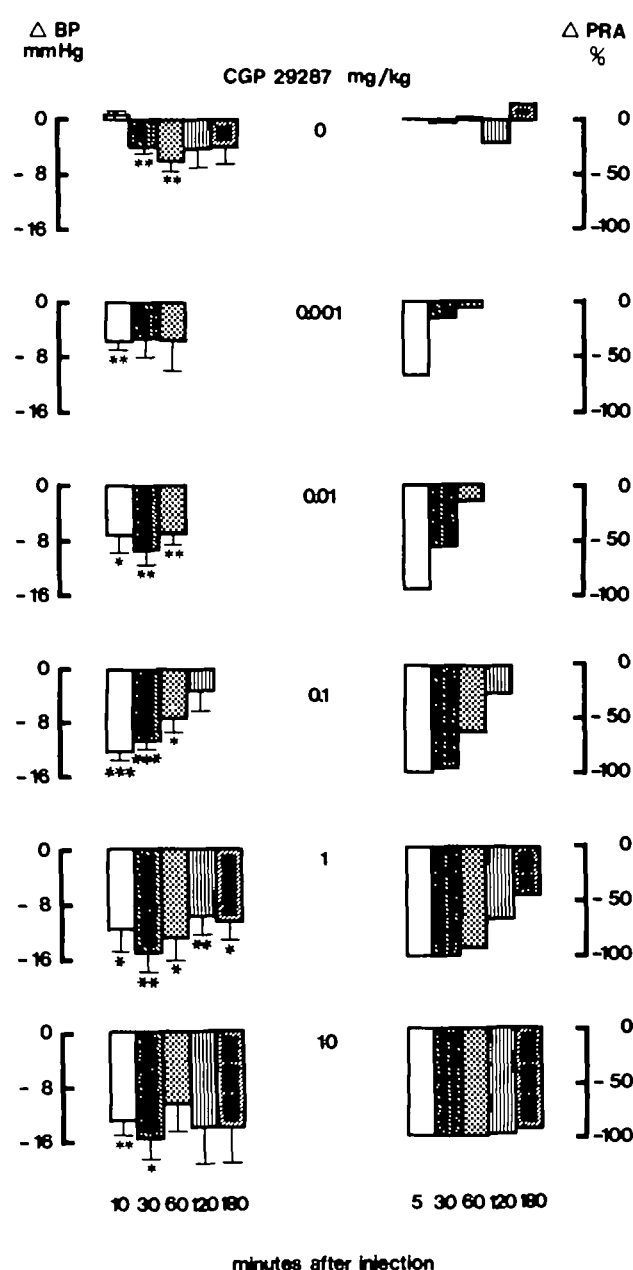


FIGURE 5. Mean changes in blood pressure (BP) and plasma renin activity (PRA) after intravenous bolus injection of saline ($n = 6$) or CGP 29 287 in doses of 0.001 ($n = 4$), 0.01 ($n = 6$), 0.1 ($n = 5$), 1.0 ($n = 7$), or 10 ($n = 4$) mg/kg. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Following oral administration of saline, blood pressure was unchanged during the first 30 minutes, but thereafter a small, progressive decrease occurred (blood pressure change at 30, 60, and 120 min = $+2 \pm 7$, -5 ± 2 , and -8 ± 4 mm Hg). Blood pressure decreased after oral application of CGP 29 287 in a dose of 100 mg/kg; the maximum response occurred within 30 minutes (Figure 7). After 120 minutes, blood pressure had recovered to values observed in control marmosets. The PRA remained unchanged over the

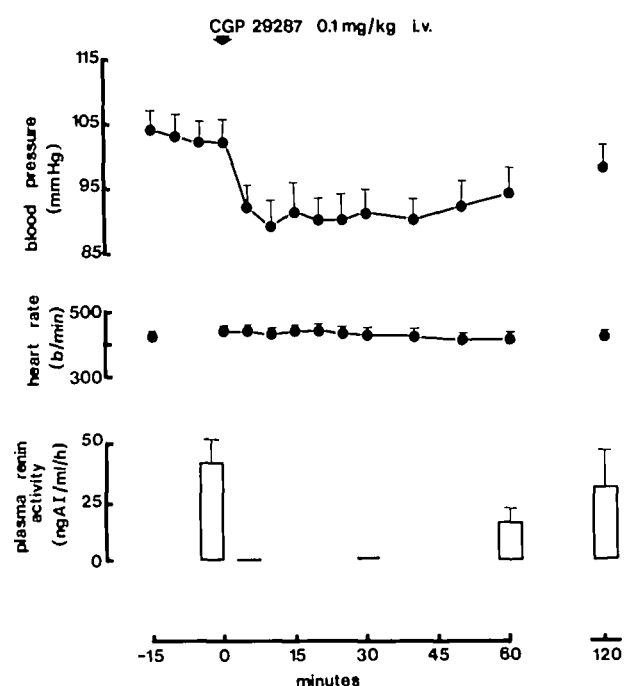


FIGURE 6. Mean arterial blood pressure, heart rate, and plasma renin activity in five furosemide-treated marmosets after intravenous bolus injection of CGP 29 287, 0.1 mg/kg. AI = angiotensin I.

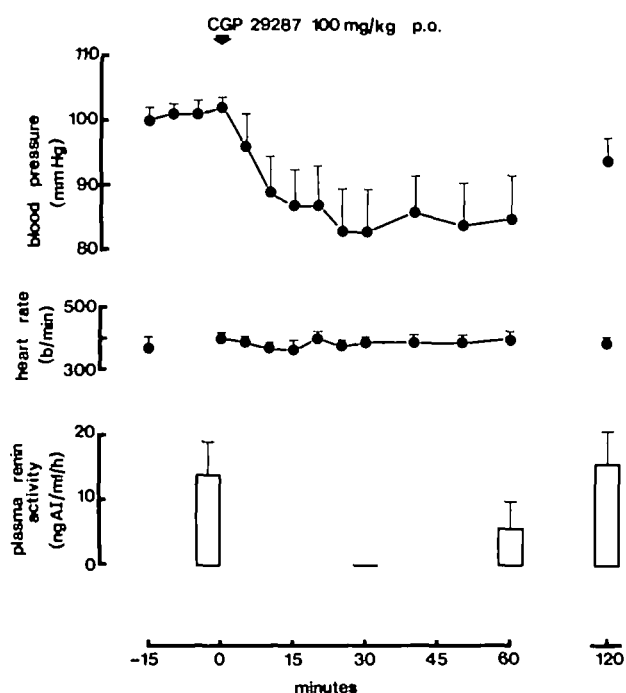


FIGURE 7. Mean arterial blood pressure, heart rate, and plasma renin activity in four furosemide-treated marmosets after oral administration of CGP 29 287, 100 mg/kg. AI = angiotensin I.

first 30 minutes after oral administration of saline and thereafter decreased (21 ± 8 , 32 ± 8 , 28 ± 5 , and 26 ± 5 ng ANG I/ml/hr at 0, 30, 60, and 120 min). The PRA was completely inhibited 30 minutes after oral administration of CGP 29 287 and had fully recovered after 120 minutes (see Figure 7). The oral dose of CGP 29 287 had no significant effect on heart rate (see Figure 7).

Tenoprotide (2 mg/kg i.v.) lowered blood pressure in furosemide-treated marmosets (-16 ± 2 mm Hg; $p < 0.01$; Figure 8) to a similar extent as CGP 29 287 (0.1 mg/kg/min; see Figure 4). Infusion of CGP 29 287 after injection of tenoprotide had no additional influence on blood pressure (see Figure 8). Tenoprotide and CGP 29 287 had no significant influence on heart rate.

The mean pressor response to ANG I was 40 ± 2 mm Hg before and 42 ± 3 mm Hg during infusion of CGP 29 287 (0.1 mg/kg/min). The mean pressor response to ANG II was 26 ± 3 mm Hg before and 33 ± 4 mm Hg during infusion of CGP 29 287. Differences between the responses before and after infusion were not significant.

Effects in Untreated and Nephrectomized Marmosets

In marmosets that were not pretreated with furosemide, the hypotensive response during infusion of CGP 29 287 (0.1 mg/kg/min) was variable and the mean fall in blood pressure (-6 ± 4 mm Hg at 30 min, $p > 0.2$) was less than in furosemide-treated animals (-14 ± 1 mm Hg; $p < 0.001$; see Figure 3). The blood pressure was stable in untreated marmosets that received saline only (blood pressure change at 30 min = -1 ± 2 mm Hg). The PRA was approximately fourfold lower in untreated (9 ± 3 ng ANG I/ml/hr) than furosemide-treated (39 ± 9 ng ANG I/ml/hr) marmosets and was completely inhibited during infusion of CGP 29 287 in both groups.

The blood pressure was unchanged 30 minutes after injection of CGP 29 287 in marmosets 1 day after bilateral nephrectomy (0 ± 4 mm Hg after 1 mg/kg

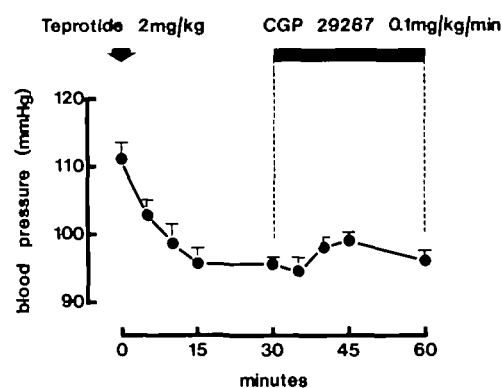


FIGURE 8. Mean arterial blood pressure in four furosemide-treated marmosets; effects of infusion of CGP 29 287 (0.1 mg/kg/min i.v.) after injection of the converting enzyme inhibitor tenoprotide (2 mg/kg i.v.).

and -1 ± 3 mm Hg after 10 mg/kg). The PRA before nephrectomy was 22 ± 6 ng ANG I/ml/hr and was unmeasurable 1 day after nephrectomy.

Discussion

Our results indicate that CGP 29 287 is a potent and specific inhibitor of primate renin *in vitro*. The specificity of inhibition is consistent with the known species differences in the structures of renin¹⁵ and angiotensinogen¹⁶ and in the specificity of renin for its substrate.^{1, 17} The transition state mimic appears to be an important determinant of the specificity of a renin inhibitor. H-142, an analogue containing the reduced scissile bond of human angiotensinogen as a transition state mimic, is a more specific inhibitor of primate renin than is CGP 29 287.⁷ It can be expected that analogues containing statine as the mimic might be less enzyme specific. Statine is derived from pepstatin, which is a less potent inhibitor of human renin than of other aspartic proteases.¹⁸ The amino acid sequence immediately adjacent to the transition state mimic appears to be another important determinant of the specificity. Other statine-containing analogues, such as SCRIP, which less closely resemble the amino acid sequence of human angiotensinogen on the C-terminal side of the mimic, are much less species and enzyme specific than CGP 29 287.^{8, 10} Species specificity of renin inhibitors limits their experimental application *in vivo*; however, enzyme specificity is important if these compounds are to be used experimentally for specific blockade of the RAS.

In vivo, CGP 29 287 also proved to be a potent inhibitor of renin. After intravenous infusion in conscious, furosemide-treated marmosets, CGP 29 287 completely inhibited PRA and lowered blood pressure in a dose as low as 0.001 mg/kg/min. CGP 29 287 was also effective after intravenous bolus injection. A small but significant hypotensive response associated with partial inhibition of PRA was observed with a dose as low as 0.001 mg/kg. The maximum response was observed with doses of 0.1 mg/kg. Higher doses were no more effective, but the response persisted longer.

The prolonged duration of action of CGP 29 287 after intravenous infusion and bolus injection is in contrast to that found with other renin inhibitors. H-142 is only effective during intravenous infusion in furosemide-treated marmosets, and blood pressure recovers within minutes after stopping the infusion.¹¹ Similarly, H-77 and SCRIP lower blood pressure during intravenous infusion in sodium-depleted dogs and blood pressure recovers within minutes after stopping the infusion.^{9, 10} The structural feature of CGP 29 287 that appears to be responsible for its increased half-life *in vivo* is the protection groups at both terminals. CGP 29 291, a renin inhibitor with the same structure as CGP 29 287 but without protection groups, has a much shorter duration of action.¹⁹ CGP 29 287 was also effective after oral administration in a high dose of 100 mg/kg. This effect is probably a consequence of the increased stability of this compound.

The hypotensive action of CGP 29 287 appears to be due entirely to blockade of the RAS. Blockade of the RAS by pretreatment with a converting enzyme inhibitor completely prevented the hypotensive response to CGP 29 287. Furthermore, CGP 29 287 did not reduce the pressor response to ANG I or ANG II, which indicates that its only action on the RAS is to inhibit renin. Additional evidence that the hypotensive response to CGP 29 287 was due entirely to inhibition of renin comes from the close relation between blood pressure and PRA. Firstly, the hypotensive response to CGP 29 287 depended on the initial activity of the RAS; it was abolished if circulating renin was eliminated by bilateral nephrectomy and was reduced if renin release was not stimulated by diuretic pretreatment. Secondly, after administration of CGP 29 287, near complete inhibition of PRA was always associated with a significant fall in blood pressure. Finally, there was a close association between recovery of blood pressure and PRA. After all doses and routes of administration of CGP 29 287, blood pressure and PRA recovery followed a similar time course. Therefore, the acute hypotensive response to CGP 29 287 in furosemide-treated marmosets appears to be specifically mediated by inhibition of PRA.

The close association between the fall in blood pressure and inhibition of PRA with CGP 29 287 is in contrast to the effects of SCRIP in sodium-depleted dogs.¹⁰ Much higher doses of SCRIP than those needed for maximum inhibition of PRA were necessary to obtain the maximum fall in blood pressure. In addition, after stopping an infusion of SCRIP, blood pressure recovered much more rapidly than PRA. The proposed explanation for this dissociation was that inhibition of tissue renin may be more important than inhibition of PRA. There may be a difference in the relative roles of plasma and tissue renin between the different animal models used to test CGP 29 287 and SCRIP. In our experiments renin was stimulated acutely, whereas in the experiments of Blaine and colleagues¹⁰ renin was stimulated chronically. However, after converting enzyme inhibition, where tissue enzyme inhibition has been shown to be more important than plasma enzyme inhibition, blood pressure recovers much more slowly than plasma enzyme activity.²⁰ This dissociation is in the opposite direction from that seen with SCRIP. Another explanation for the dissociation observed with SCRIP may be that in higher doses SCRIP has a depressor effect that is unrelated to inhibition of renin. A comparison of SCRIP and CGP 29 287 in the same model would be necessary to clarify this point.

In summary, our results suggest that CGP 29 287 is an inhibitor of primate renin with high potency and specificity both *in vitro* and *in vivo*. In furosemide-treated marmosets, CGP 29 287 lowered blood pressure and inhibited PRA without changing heart rate. This hypotensive response appears to be due entirely to inhibition of renin. CGP 29 287 has a prolonged duration of action in comparison to previously described renin inhibitors. We found that it is effective not only

after intravenous infusion but also after intravenous bolus injection. Moreover, CGP 29 287 was orally active in a high dose. Our results indicate that CGP 29 287 is a useful compound for experimental studies in vivo on the effects of specific and prolonged blockade of the RAS.

Acknowledgments

We thank Drs. Peter Bühlmyer and Bernhard Riniker for the synthesis of CGP 29 287. The excellent technical assistance of Miss Guri Christiansen, Mrs. Michele Lartigot, and Mrs. Elizabeth Scheidegger and the secretarial help of Miss Claudia Metzger are gratefully acknowledged.

References

- Ondetti MA, Cushman DW. Enzymes of the renin-angiotensin system and their inhibitors. *Annu Rev Biochem* 1982;51:283-308
- Hofbauer KG, Wood JM. Inhibition of renin: recent developments. *Contrib Nephrol* 1984;43:144-152
- Gross F, Lazar J, Orth H. Inhibition of the renin-angiotensinogen reaction by pepstatin. *Science* 1972;175:656
- Poulsen K, Burton J, Haber E. Competitive inhibitors of renin. *Biochemistry* 1973;12:3877-3882
- Burton J, Cody RJ, Herd JA, Haber E. Specific inhibition of renin by an angiotensinogen analog: studies in sodium depletion and renin-dependent hypertension. *Proc Natl Acad Sci USA* 1980;77:5476-5479
- Ngo TT, Tunnicliff G. Inhibition of enzymatic reactions by transition state analogs: an approach for drug design. *Gen Pharmacol* 1981;12:129-138
- Szelke M, Leckie B, Hallett A, Jones DM, Sueiras J, Atrash B, Lever AF. Potent new inhibitors of human renin. *Nature* 1982;299:555-557
- Boger J, Lohr NS, Ulm EH, et al. Novel renin inhibitors containing the amino acid statine. *Nature* 1983;303:81-84
- Szelke M, Leckie BJ, Tree M, et al. H-77: a potent new renin inhibitor: in vitro and in vivo studies. *Hypertension* 1982;4(suppl II):II-59-II-69
- Blaine EH, Schorn TW, Boger J. Statine-containing renin inhibitor: dissociation of blood pressure lowering and renin inhibition in sodium-deficient dogs. *Hypertension* 1984;6(suppl I):I-111-I-118
- Wood JM, Forgiarini P, Hofbauer KG. Inhibition of renin and converting enzyme in conscious volume-depleted marmosets. *J Hypertension* 1983;1(suppl 2):189-191
- Webb DJ, Cumming AMM, Leckie BJ, Lever AF, Morton JJ, Robertson JIS. Reduction of blood pressure in man with H-142, a potent new renin inhibitor. *Lancet* 1983;2:1486-1487
- Hackenthal E, Hackenthal R, Hofbauer KG. No evidence for product inhibition of the renin-angiotensinogen reaction in the rat. *Circ Res* 1977;41(suppl II):II-49-II-54
- Michel J-B, Wood JM, Hofbauer KG, Corvol P, Ménard J. Blood pressure effects of renin inhibition by human renin antiserum in normotensive marmosets. *Am J Physiol* 1984;246:F309-F316
- Imai T, Miyazaki H, Hirose S, et al. Cloning and sequence analysis of cDNA human renin precursor. *Proc Natl Acad Sci USA* 1983;80:7405-7409
- Tewksbury DA. Angiotensinogen. *Fed Proc* 1983;42:2724-2728
- Poulsen K, Haber E, Burton J. On the specificity of human renin: studies with peptide inhibitors. *Biochim Biophys Acta* 1976;452:533-537
- Aoyagi T, Morishima H, Nishizawa R, Kunitomo S, Takeuchi T, Umezawa H. Biological activity of pepstatins, pepstanone A and partial peptides on pepsin, cathepsin D and renin. *J Antibiot (Tokyo)* 1972;25:689-694
- Wood JM, Fuhrer W, Bühlmyer P, Riniker B, Hofbauer KG. Protection groups increase the in vivo stability of a statine containing renin inhibitor. In: Kostka V, ed. *Aspartic proteinases and their inhibitors*. Berlin, New York: Walter de Gruyter, 1985
- Unger T, Ganten D, Lang RE, Schölkens BA. Persistent tissue converting enzyme inhibition following chronic treatment with Hoe 498 and MK 421 in spontaneously hypertensive rats. *J Cardiovasc Pharmacol* 1985;7:36-41

Effects of a specific and long-acting renin inhibitor in the marmoset.

J M Wood, N Gulati, P Forgiarini, W Fuhrer and K G Hofbauer

Hypertension. 1985;7:797-803

doi: 10.1161/01.HYP.7.5.797

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 1985 American Heart Association, Inc. All rights reserved.

Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/content/7/5/797>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Hypertension* is online at:
<http://hyper.ahajournals.org/subscriptions/>