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Remikiren (Ro 42-5892)—An Orally Active Renin Inhibitor in Essential Hypertension

Effects on Blood Pressure and the Renin-Angiotensin-Aldosterone System

Anders Himmelmann, Anders Bergbrant, Anders Svensson, Lennart Hansson, and Mattias Aurell

Remikiren (Ro 42-5892) is a new orally active renin inhibitor with high potency and specificity in vitro. In the present study, the drug was given in a short-term study in patients with essential hypertension, either as monotherapy or with added hydrochlorothiazide. Following a wash-out period of at least 3 weeks and then 8 days of single-blind placebo, 29 patients with essential hypertension were given remikiren 600 mg orally for 8 days. After 4 days of remikiren, hydrochlorothiazide 12.5 mg or 25 mg or placebo was added in double-blind fashion for the last 4 days. There were no significant changes in blood pressure in patients given remikiren alone. In patients given additional hydrochlorothiazide for 4 days, a marked reduction in blood pressure was observed. Remikiren effectively inhibited the plasma renin activity 24 h post-dose, whereas angiotensin II was reduced only during the first hours after drug administration. It is concluded that remikiren is orally effective. Its antihypertensive effect during short-term administration was not significant, but when given with a diuretic, a marked potentiation occurred. Further studies are needed to establish the long-term effects of remikiren alone and in combination therapy. Am J Hypertens 1996;9:517–522

KEY WORDS: **Blood pressure, hydrochlorothiazide, hypertension, remikiren (Ro 42-5892), renin-angiotensin-aldosterone system.**

The renin-angiotensin-aldosterone system has been suggested to be of importance for both the development of hypertension and the complications of high blood pressure.[1,2] Although not proven in essential hypertension,[2] it has been suggested, based on several independent and complementary lines of evidence, that blockade of the renin-angiotensin-aldosterone system with an angiotensin-converting enzyme (ACE) inhibitor may have cardioprotective or vasculoprotective effects.[3,4] However, dry cough and angioedema are well known side effects of ACE inhibitors.[5–7] A possible mechanism for these adverse reactions may be the accumulation of bradykinin, which is degraded by ACE.[5–7] Thus, at least with regard to side effects, there may be potential advantages with alternative routes of blocking the renin-angiotensin-aldosterone system.[8,9]

Remikiren (Ro 42-5892) is a new renin inhibitor with high potency and specificity in vitro.[9–13] It is a peptide mimetic inhibitor of renin, and it inhibits human renin activity in the subnanomolar range. We have tested this drug, given orally, in a short-term study and evaluated its effects on blood pressure and

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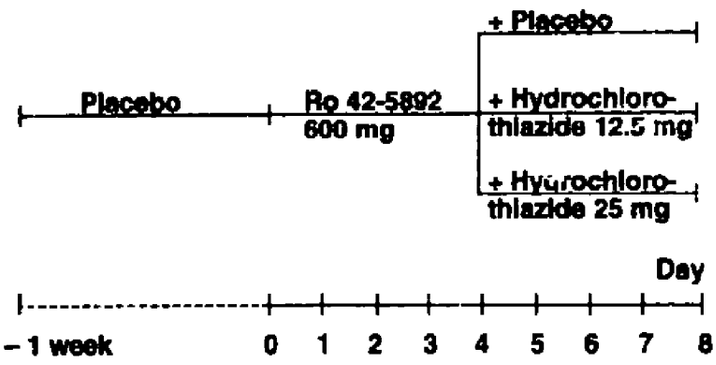

FIGURE 1. *Study design.*

the renin-angiotensin-aldosterone system in patients with essential hypertension, either as monotherapy or with added hydrochlorothiazide.

MATERIAL AND METHODS

After exclusion of secondary forms of hypertension, 29 patients with essential hypertension (Table 1) entered a washout period of at least 3 weeks.[14] This was followed by 8 days of placebo, and then all patients were given remikiren 600 mg orally for 8 days. After 4 days of remikiren, hydrochlorothiazide 12.5 mg, 25 mg or placebo was added in double-blind fashion for the last 4 days (Figure 1).

Blood pressure was measured in the recumbent position following 5 minutes of rest using a mercury sphygmomanometer. Its cuff contained a balloon with the dimensions 12 × 35 cm. The disappearance of the Korotkoff sounds (phase V) was taken as the diastolic blood pressure.

Blood samples were taken 24 to 26 h postdose at baseline and after 4 and 8 days of treatment with remikiren. On day 4, blood samples were also taken at the time of drug administration and after 30, 60, 180, and 360 min, respectively. Plasma renin activity, plasma renin concentration, angiotensin II, angiotensinogen, aldosterone and ACE activity were measured with radioimmunoassay, as previously described.[15]

Urine was collected for 24 h at baseline and after 4 and 8 days of active treatment. The sodium content was determined by flame photometry and the 24-h sodium excretion was calculated.

Values are given as means ± SEM. To analyze differences from baseline within the groups, a two-sided paired Student's *t* test was used. Differences between the groups were analyzed with a two-sided unpaired Student's *t* test. As there were no differences in blood pressure response between patients given an additional 12.5 mg or 25 mg hydrochlorothiazide, those two groups were combined in the analyses. The degree of linear relationship between two variables was described using Pearson's correlation coefficients. A $P < .05$ was considered significant.

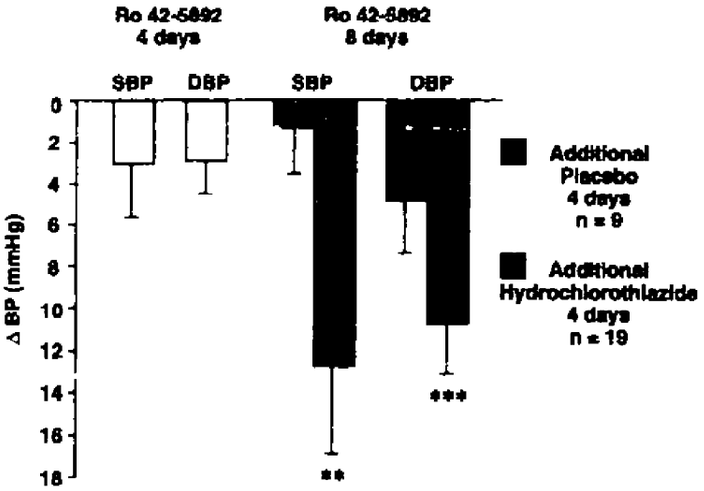

FIGURE 2. *Changes (mean; SEM) in blood pressure (Δ BP), systolic (SBP) and diastolic (DBP), after 4 and 8 days treatment with remikiren (Ro 42-5892) and the addition of either hydrochlorothiazide or placebo after 4 days.* **P < .01; ***P < .001.

The study was approved by the Ethical Committee of the Medical Faculty of Göteborg University.

RESULTS

There were no significant drops in systolic blood pressure (−3.0 ± 2.5 mm Hg) or in diastolic blood pressure (−2.9 ± 1.5 mm Hg) after 4 days on remikiren. After 8 days on remikiren, there were still no significant decreases in systolic blood pressure (−1.1 ± 2.1

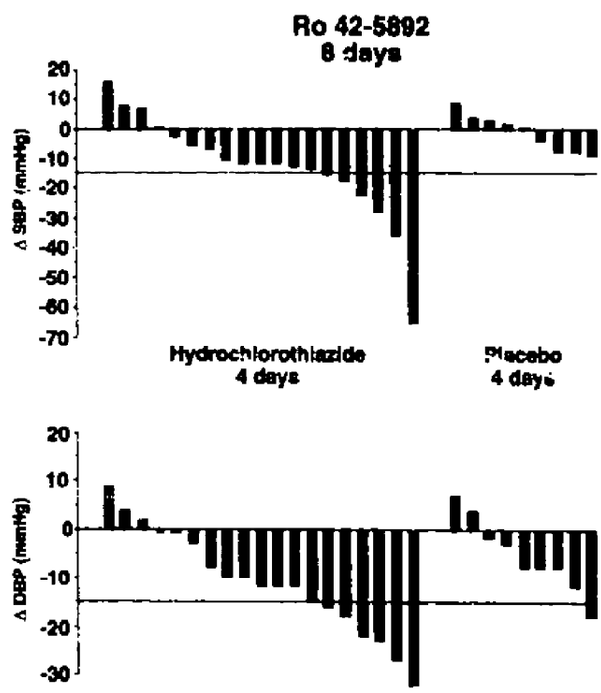

FIGURE 3. *Individual changes in systolic blood pressure (Δ SBP) and diastolic blood pressure (Δ DBP) with the addition of either hydrochlorothiazide or placebo for 4 days, after initial 4-day treatment with remikiren (Ro 42-5892).*

TABLE 1. BASELINE CHARACTERISTICS OF 29 PATIENTS (26 MEN, 3 WOMEN) WITH ESSENTIAL HYPERTENSION (MEAN ± SEM)

Age (years)	57 ± 1.3
Height (cm)	177.8 ± 1.7
Weight (kg)	88.9 ± 2.4
BMI (kg/m^2)	28.9 ± 0.7
SBP (mm Hg)	151.0 ± 3.1
DBP (mm Hg)	94.4 ± 1.1
HR (beats/min)	68.4 ± 1.3

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

mm Hg) or in diastolic blood pressure (−5.3 ± 2.6 mm Hg) in patients given only remikiren. In patients receiving additional hydrochlorothiazide during day 5 to day 8, systolic blood pressure and diastolic blood pressure decreased significantly (−12.8 ± 4.1 mm Hg; $P < .01$ and −10.8 ± 2.5 mm Hg; $P < .001$, respectively). Changes in blood pressure are illustrated in Figure 2, and individual changes in systolic blood pressure and diastolic blood pressure are illustrated in Figure 3.

The heart rate was unaffected by remikiren after 4 and 8 days of treatment (−1.0 ± 1.3 beats/min and −6.1 ± 1.4 beats/min, respectively). There were no significant differences with regard to change in heart rate between the treatment groups at the end of the study (−7.6 ± 1.5 beats/min *v* −2.7 ± 2.7 beats/min; $P = .1$).

Body weight was slightly reduced from baseline to day 8 (−0.43 ± 0.15 kg; $P < .01$) in the whole study group. However, there were no significant differences with regard to change in body weight between the patients who received additional hydrochlorothiazide and those who were given additional placebo (−0.48 ± 0.20 *v* −0.31 ± 0.13 kg; $P = .60$).

The 24-h sodium excretion did not change significantly during the study period (Table 2), and there were no significant differences with regard to sodium loss between the treatment groups (25.2 ± 33.4 *v* 1.2 ± 16.5 mmol/24 h; $P = .60$ in the hydrochlorothiazide and placebo groups, respectively).

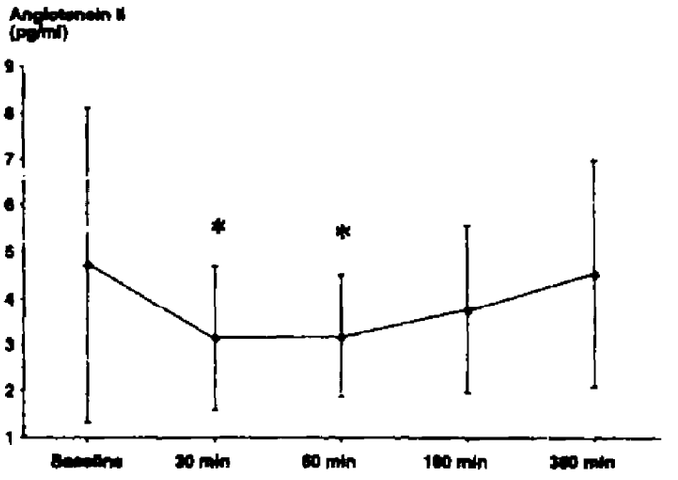

FIGURE 4. *Level of angiotensin II (±SD) after 4 days of treatment with remikiren (Ro 42-5892) at time of drug administration (Baseline) and 30, 60, 180 and 360 min after dose intake, respectively.* *$P < .05$.

The activity of the renin-angiotensin-aldosterone system in all patients studied, at baseline and after 4 and 8 days of treatment with remikiren, are given in Table 2. There was a significant drop in plasma renin activity after 4 and 8 days. Plasma renin concentration rose significantly from baseline to the end of the study, while angiotensinogen and aldosterone both fell significantly.

On day 4, angiotensin II was significantly reduced 30 and 60 min after drug administration (−1.7 ± 0.7 pg/mL and −1.6 ± 0.7 pg/mL, respectively), but had returned to baseline levels 3 h after dose intake (Figure 4). Plasma renin activity, plasma renin concentration, aldosterone, or angiotensin converting enzyme (ACE) activity did not change significantly during the first 6 h postdose on day 4.

There was a reduction in ACE concentration in patients receiving hydrochlorothiazide in addition to remikiren as compared to those who were given addi-

TABLE 2. SODIUM (Na) EXCRETION AND ACTIVITY OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN ALL PATIENTS STUDIED, AT BASELINE AND AFTER 4 AND 8 DAYS OF TREATMENT WITH REMIKIREN (Ro 42-5892) (MEAN ± SEM)

	Baseline	4 Days	8 Days
Na excretion (mmol/24 h)	145.7 ± 11.8	138.6 ± 8.2	158.3 ± 12.4
PRA (ng/mL/h)	0.52 ± 0.11	0.28 ± 0.10†	0.11 ± 0.01†
PRC (μGU/mL)	11.9 ± 1.83	16.7 ± 4.02	22.7 ± 3.72†
A II (pg/mL)	4.5 ± 0.53	4.7 ± 0.64	4.8 ± 0.50
Angiotensinogen (ng/mL)	3573 ± 159	3092 ± 281	2870 ± 286*
Aldosterone (pg/mL)	0.35 ± 0.03	0.35 ± 0.03	0.25 ± 0.03†
ACE (units)	43.0 ± 2.0	43.0 ± 1.9	40.6 ± 1.7

PRA, plasma renin activity; PRC, plasma renin concentration; AII, angiotensin II; ACE, angiotensin converting enzyme.
Significance test versus baseline values. *$P < 0.05$; †$P < .01$.

TABLE 3. ACTIVITY OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM, AT THE END OF THE STUDY, IN PATIENTS RECEIVING HYDROCHLOROTHIAZIDE (Htz) OR PLACEBO IN ADDITION TO REMIKIREN (Ro 42-5892) (MEAN ± SEM)

	Additional Htz	Additional Placebo
PRA (ng/mL/h)	0.12 ± 0.01	0.1 ± 0.00
PRC (μGU/mL)	23.2 ± 4.3	21.6 ± 8.0
A II (pg/mL)	5.0 ± 0.65	4.4 ± 0.66
Angiotensinogen (ng/mL)	2852 ± 383	2915 ± 330
Aldosterone (pg/mL)	0.25 ± 0.03	0.23 ± 0.06
ACE (units)	42.9 ± 1.7	35.4 ± 3.7

PRA, plasma renin activity; PRC, plasma renin concentration; AII, angiotensin II; ACE, angiotensin converting enzyme.

tional placebo (Table 3). Besides this finding there were no significant differences in the activity of the renin-angiotensin-aldosterone system in patients in either treatment group. Changes in the activity of the renin-angiotensin-aldosterone system from baseline to the end of the study in all patients studied are illustrated in Figure 5. There were no significant correlations between baseline plasma renin activity and change in systolic blood pressure ($r = 0.12$; $P = .5$) or diastolic blood pressure ($r = 0.26$, $P = .17$). No relationships were found between baseline angiotensin II concentration and change in blood pressure ($r = 0.13$; $P = .5$, for both systolic and diastolic blood pressure).

No serious adverse events occurred. No patients were withdrawn due to side effects. Two patients experienced dizziness, and there were two complaints of mild gastrointestinal symptoms.

DISCUSSION

The present short-term study demonstrates that remikiren is orally active. Remikiren blocks the plasma renin activity effectively and, in combination with hydrochlorothiazide, it lowers blood pressure.

Remikiren inhibits the renin-angiotensin-aldosterone system without affecting ACE, and thus offers an alternative way for lowering blood pressure.[9–11] Effective renin inhibitors need to have high affinity for renin and good bioavailability.[9] A major problem with previous renin inhibitors has been their poor absorption from the gastrointestinal tract.[9–11]

Although a clear reduction in plasma renin activity was observed in the present study, the blood pressure effect after 4 days of oral administration was not statistically significant. After 4 more days of remikiren as monotherapy, five out of nine patients had at least an 8 mm Hg reduction in diastolic blood pressure. It is conceivable that the effect on blood pressure takes longer to be fully developed as is the case for ACE inhibitors[16] and angiotensin II antagonists.[17] However, in patients given additional hydrochlorothiazide for 4 days, a marked reduction in both systolic and diastolic blood pressure was observed.

In the absence of a group given only hydrochlorothiazide, it is not possible to differentiate the effects of remikiren and hydrochlorothiazide. However, the impressive reduction of diastolic blood pressure after the addition of hydrochlorothiazide for only 4 days is greater than would be expected with hydrochlorothiazide alone.[15,18] Moreover, sodium depletion is also known to increase the hypotensive response to both ACE inhibitors and angiotensin II antagonists.[16,19]

A reduction in angiotensin II levels was seen during the first hour post-dose on the fourth day of treatment with remikiren. This finding is in agreement with a previous study in normal volunteers who were given doses of remikiren ranging from 100 mg to 1200 mg.[20] In the latter study, no effect on blood pressure was observed. However, the plasma renin activity and angiotensin II fell to their nadir within 30 min after drug intake and, in accordance with our findings, the decrease in angiotensin II lasted for maximally 2 h. The blood pressure lowering effect of remikiren observed in the present study and in other studies[21–23] may point to a regional inhibition of renin not reflected by plasma angiotensin levels. Alternatively, it could indicate inhibition of aldosterone secretion or nonspecific, renin-independent effects.[9] Moreover, it has been demonstrated by Derkx et al that the nonparallel effects of renin inhibitor treatment on plasma renin activity and the plasma levels of angiotensin II, as well as on blood pressure, may be an assay-related artifact, which may mislead the observer into overestimating the magnitude of drug effect.[24]

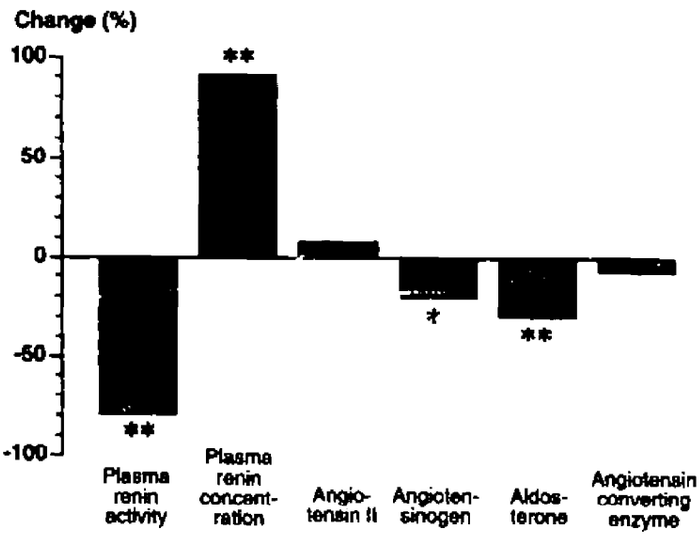

FIGURE 5. *Changes in the activity of the renin-angiotensin-aldosterone system from baseline to day 8 of the study in all patients studied.* *P < .05; **P < .01.

In a single-dose study by van den Meiracker et al, remikiren was given as an oral dose to 6 patients who were not sodium depleted.[21] At variance with our findings, a blood pressure reducing effect was observed in these patients with normal sodium balance; but in agreement with our findings, the effect on blood pressure was observed over a longer period than its effect on angiotensin II. In a double-blind placebo controlled study in hypertensive patients, remikiren 600 mg was given once daily for 8 days.[22] Sitting diastolic blood pressure fell significantly, by 5 mm Hg at trough, as compared to placebo. In a recent study in patients with essential hypertension treated with remikiren 100 mg once daily, a significant reduction in blood pressure was observed.[23] From the latter study it was also concluded that the duration of treatment appears to be an important determinant of the efficacy of remikiren.

In the present study, remikiren was generally well tolerated. Two patients experienced mild gastrointestinal symptoms. In another study, which investigated the tolerability of remikiren, ascending doses up to 1600 mg orally were given.[12] The compound was well tolerated except at the 1600 mg oral dose level, at which diarrhea occurred in two subjects.[12]

In conclusion, the present study demonstrates that the renin inhibitor remikiren is orally active and well tolerated in patients with essential hypertension. Given as monotherapy for 8 days, no significant antihypertensive effect could be demonstrated; but with added hydrochlorothiazide, impressive blood pressure reductions of more than 15 mm Hg diastolic in just 4 days were seen in more than 35% of the patients. It is clear that further studies are needed to establish the long-term effects of remikiren used alone and in combination therapy.

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