Antihypertensive Effect of Orally Administered Glandular Kallikrein in Essential Hypertension

Results of a Double Blind Study

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SUMMARY The antihypertensive effect of oral administration of pig pancreatic kallikrein was investigated in a double blind study of 20 patients with essential hypertension. Kallikrein treatment lowered the blood pressure (BP) significantly from 159.5/104.5 to 146.1/92.8 mm Hg in the supine and from 153/106.1 to 136.1/95.6 mm Hg in the standing position. Blood pressure remained unchanged in the placebo group. Urinary kallikrein, sodium excretion, and GFR increased with treatment, but these changes did not reach statistical significance. In the kallikrein-treated patients but not in the placebo group, urinary kallikrein was correlated both to GFR \( r = 0.7, p < 0.001 \) and sodium excretion \( r = 0.5, p < 0.01 \). The antihypertensive mechanism of kallikrein treatment remains unknown. It could be speculated that kallikrein may induce changes in local blood flow, mediated by kinin and prostaglandin release. (Hypertension 3 (suppl I): 1-18—1-21, 1981)

KEY WORDS urinary kallikrein excretion essential hypertension kallikrein treatment

Patients and Methods

Twenty patients (9 females, 11 males) with mild-to-moderate sustained essential hypertension (diastolic BP, 95–120 mm Hg) were included in the study. They ranged in age from 22 to 55 years (mean age, 37.8 years) and had not taken antihypertensive drugs previously. Prior to the study, all patients were examined to exclude secondary hypertension. All patients had normal renal function (serum creatinine below 95 \( \mu \)mole/liter; glomerular filtration rate (GFR) above 80 ml/min). Throughout the study the patients remained on an unrestricted salt and fluid intake. All subjects were studied as outpatients. A written informed consent was obtained from each patient.

After a placebo period of 4 weeks (control period), the patients received either a pure preparation of pig pancreatic kallikrein (200 biological units three times per day in gastric juice resistant tablets; Bay d7687, Bayer AG, Leverkusen, West Germany) \( n = 10 \) or placebo \( n = 10 \) in a double blind fashion. No other medication was taken by any of the patients. The patient compliance was assessed by weekly pill countings and was similar in both groups of patients. Blood pressure and pulse rate were measured weekly after 5 minutes in the supine and 3 minutes in the standing
position. Each BP recording was the mean of two measurements; all BP measurements were made by the same investigator (A.O.). The 24-hour urine samples were collected at the end of the control period and during the second and fourth week of treatment. On the days of urine collection, blood was withdrawn after 2 hours of recumbency for the measurement of plasma renin activity (PRA), plasma aldosterone concentration, and serum creatinine levels.

Urinary kallikrein activity was measured by hydrolysis of the chromogenic substrate H-D-Val-Leu-Arg-pNA (S2266, AB Kabi, Moelndal, Sweden) using a modification of the method of Amundsen et al. The PRA and plasma aldosterone concentration were determined by radioimmunoassay. Urinary sodium and potassium were measured by flame photometry, creatinine in serum and urine by autoanalyzer. Data were analyzed by Student's paired and unpaired t test and linear regression analysis (Hotelling-Pabst test). An initial analysis of variance showed that repeated t test analysis was valid. Differences were considered significant at the \( p < 0.05 \) level. Results are expressed as the mean ± SEM.

### Results

The BP and biochemical parameters were similar in the kallikrein and placebo groups at the end of the control period (figs. 1, 2; table 1). After 4 weeks of kallikrein treatment, mean systolic and diastolic BP had decreased from 159.5 ± 4.7/104.5 ± 2.2 to 146.3 ± 6.6/92.8 ± 3.3 mm Hg in the supine and from 153 ± 3.5/106.1 ± 1.9 to 136.1 ± 3.6/95.6 ± 2.3 mm Hg in the standing position (figs. 1, 2). These changes were significant when compared to control values and to the data obtained in the placebo group (figs. 1, 2). The BP drop was already seen after 1 week, and there was a gradual further decrease until the end.
Discussion

The data show that orally administered glandular (pig pancreatic) kallikrein lowers the BP in patients with mild-to-moderate essential hypertension in a double blind study. This confirms our previous results, which were obtained in an open trial. The reduction of BP was similar in both studies. Urinary kallikrein excretion during the control period in the 20 hypertensive patients studied was significantly (p < 0.01) decreased when compared to our previously reported values in normotensive subjects (0.73 ± 0.11 vs 1.26 ± 0.14 EU/24 hrs). Similar results were obtained by other investigators.

In contrast to all antihypertensive drugs, kallikrein is a naturally occurring substance in man. The urinary excretion of this substance seems to be lower in essential hypertension. This suggests that a defect in the renal kallikrein-kinin system may be involved in the pathogenesis and/or pathophysiology of this disease in some patients. However, the antihypertensive mechanism of glandular kallikrein is unknown at the present time. It could be argued that the oral administration of pig pancreatic kallikrein, a protein with a molecular weight of 25,000, is able to produce systemic effects and/or localized changes not only within the gastrointestinal tract but also in other organs such as the kidneys. This latter suggestion is supported by the present and earlier reported findings of an increase in GFR and kallikrein excretion with kallikrein treatment. In the previous study, both changes were significant in the patients with very low (below 0.5 EU/24 hr) but not in those with normal or only slightly reduced kallikrein excretion. This subdivision was not possible in the present investigation because of the smaller number of patients receiving kallikrein treatment. The rise in urinary kallikrein during treatment in the previous study was due to excretion of endogenous kallikrein, because pig pancreatic kallikrein could not be detected in the urine by a specific radioimmunoassay.

Our present findings of a temporary increase in urinary volume and sodium excretion with kallikrein treatment are of limited validity since salt and water intake were not restricted. Since it has been reported that kallikrein excretion depends on renal function and renal blood flow, the observed increase in urinary kallikrein may have been secondary to some changes within the kidneys. These changes might have been mediated by a treatment-induced release of kinins and prostaglandins. This is suggested by the following observations: 1) the increase in sperm motility with kallikrein treatment seems to depend on the proteolytic activity of the enzyme, because its effect was abolished by inhibition with aprin; 2) the addition of kinins to the semen specimen stimulates sperm motility immediately; and 3) intrarenal infusion of kinins increases renal blood flow, diuresis, and natriuresis. These latter effects of kinins are due in part to prostaglandin release. However, this possible action of orally administered glandular kallikrein remains hypothetical, and further study is needed to elucidate the antihypertensive mechanism of kallikrein treatment.

Acknowledgments

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