Pharmacological Studies on TA-6366, a New ACE Inhibitor: II. Effect of Long-Term Administration from the Pre-Hypertensive Stage on Blood Pressure, Relative Heart Weight and ACE Activity of Various Tissues in Spontaneously Hypertensive Rats (SHRs)

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ABSTRACT—The long-term oral administration of TA-6366 (5 mg/kg/day) from 4-weeks old impeded the genetic hypertension development with only a slight decrease in heart rate in spontaneously hypertensive rats (SHRs). However, the lower dose (1 mg/kg/day) of TA-6366 did not affect the development, but it lowered blood pressure after the development was almost accomplished. Concomitantly, relative heart weights in both the groups were markedly decreased to almost the same degree. The reduction of ACE activity in the aorta, brain and lung of both groups was found at 24 hr after the final administration, particularly at the 5 mg/kg/day dose; and that of the aorta was kept at almost the same low level even on the 9th day after withdrawal. After withdrawal of TA-6366 (5 mg/kg/day), the significant decrease in blood pressure was sustained at least for 10 weeks. The beneficial effect of TA-6366 on the hypertension development in SHRs seems to be related to its strong and long-lasting ACE inhibition, especially in the vasculature.

It has already been reported that the long-term oral administration of angiotensin I converting enzyme (ACE) inhibitors such as captopril and enalapril from 4-weeks old prevent genetic hypertension development in spontaneously hypertensive rats (SHRs) (1, 2). However, in these studies, the assessment of these drugs on the hypertension development were examined at about 5 times or more higher doses as compared with those required to lower blood pressure in adult SHRs. Additionally, if the mechanism for the preventive effects of enalapril and captopril is attributable to their ACE inhibitory action, such high doses are unnecessary, because they are well-known to have potent ACE inhibitory effects at the much lower doses.

(4S)-1-Methyl-3-[(2S)-2-[N-((1S)-1-ethoxy-carbonyl-3-phenylpropyl)amino]propionyl]-2-oxoimidazolidine-4-carboxylic acid hydrochloride (TA-6366), a newly developed ACE inhibitor, has an antihypertensive effect in adult SHRs and two-kidney, one-clip renal hypertensive rats at doses of 0.5–2 mg/kg, p.o. or more; and its effects in these hypertension animals are as potent as or more potent than
those of enalapril (3). The main purpose of the present study was to determine if TA-6366 prevents the hypertension development even at dose ranges similar to those that lower blood pressure in the above mentioned hypertensive animals and to compare its ability with that of enalapril and captopril.

MATERIALS AND METHODS

Animals and drug treatment

A total of 166 4-week old male SHRs (from Charles River Japan, Inc.), weighing 60–85 g, were used. The animals were maintained under identical conditions of temperature (23 ± 1°C), humidity (55 ± 5%) and photoperiod (12 hr on, 12 hr off); and they were allowed normal rat chow (CRF-1, Oriental Yeast Industry Co., Ltd.) and water ad libitum.

One hundred and fifty SHRs were randomly and equally divided into the following 5 groups: vehicle control (10 ml distilled water/kg/day) group, TA-6366, 1 mg/kg/day group, TA-6366, 5 mg/kg/day group, enalapril, 5 mg/kg/day group and captopril, 5 mg/kg/day group. The drugs and vehicle were administered by gavage once a day at a fixed time from 4-weeks old for 10 weeks. Each group was randomly divided into the following 4 sub-groups of 6 to 9 rats: a group for the measurement of systolic blood pressure, heart rate, water intake, urine volume, urinary electrolytes, and ACE activity in the various tissues 24 hr after the final administration; a group for the measurement of plasma renin activity and plasma angiotensin I concentration; a group for the measurement of heart and kidney weights; a group for the measurement of ACE activity in the various tissues 9 days after withdrawal.

The remaining 16 animals were randomly and equally divided into the following 2 groups to examine the duration of the blood pressure-lowering effect of TA-6366 after the withdrawal: vehicle control (10 ml distilled water/kg/day) group and TA-6366 5 mg/kg/day group. The drugs were administered for 9 weeks in the same manner as described above. After withdrawal, they were kept for 13 weeks for the measurement of systolic blood pressure.

Measurement

Blood pressure and heart rate: Systolic blood pressure and heart rate were measured by the tail cuff method and with a pulse rate meter (Nihon Kohden, AT-600G), respectively, after the rats were put into a cabin (Ueda, USM-105-R) kept at 40°C for about 10 min. These measurements were performed once a week on a fixed day immediately before each drug administration. In addition, in the groups for examining blood pressure change after withdrawal, the weekly measurement of blood pressure was continued for 13 weeks after withdrawal.

Urine volume, urinary electrolytes and water intake: Two days before the final dosing, animals were put into the metabolic cages immediately after drug administration. The volumes of water intake and urine excretion for 24 hr were measured, and urinary Na⁺ and K⁺ contents were determined with a flame photometer (Hitachi, 205D).

Heart and kidney weights: Twenty-four hr after the final dosing, the animals were bled to death under ether anesthesia. Immediately after the isolation of the heart and kidney, blood on the organs was wiped off with a filter paper and the organs were weighed.

Plasma renin activity (PRA) and plasma AT-I concentration: Six hr after the final dosing, renal arteries were occluded bilaterally with hemostatic clamps under light ether anesthesia. Blood samples were collected from the abdominal aorta and transferred to polyethylene tubes with EDTA-2Na salt. PRA and AT-I concentration were measured radioimmunologically with a commercial assay kit (Midori Juji).

ACE activity in the thoracic aorta, lung, brain and serum: Twenty-four hr after the final dosing and 9 days after withdrawal, under ether anesthesia, blood samples were collected from the abdominal aorta. Immediately after the animals were killed by exsanguination, the
Thoracic aorta, lung and brain were removed; the organs were cleaned of surrounding connective tissue and then rinsed in cold physiological saline solution. The crude enzyme solution was prepared from each tissue by the following methods. Thoracic aorta and lung: the aorta (ca. 50 mg) or lung (ca. 70 mg) tissue was homogenized in 0.5 ml of 0.01 M cold Tris-HCl buffer solution (pH 7.4) containing 0.2 M sucrose for 3 min. Brain: the left cerebral hemisphere (ca. 0.8 g) was homogenized in 1.5 ml of the same buffer solution for 1 min. All the homogenates were centrifuged (3,000 r.p.m. for 5 min), and the supernatants were used as crude enzyme solution. Serum itself was used as a crude enzyme solution.

The enzyme reaction assay was performed by the following method. 0.01 M Tris-HCl (pH 7.4), containing sodium chloride (60 μmoles), hippuryl-histidyl-leucine (0.5 μmoles) and the crude enzyme solution (1 to 25 μl) in a final volume of 0.5 ml was incubated for 30 to 120 min at 37°C and then immersed into ice-cold water to stop the enzyme reaction. Histidyl-leucine produced in the reaction medium was measured microbiologically using Leuconostac mesenteroides P-60. All assays were performed within 24 hr after their preparations to avoid the decomposition of captopril on storage (4), and each assay was run in duplicate.

Drugs

TA-6366, enalapril and captopril were synthesized at the Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., as previously reported (5-7). The other drugs used were as follows: hippuryl-histidyl-leucine (Sigma) and EDTA-2Na (Katayama).

Statistics

All the results were expressed as the mean ± S.E.M. When comparing two groups, statistical analysis was performed by Student's t-test. When comparing multiple groups, statistical analysis was performed as follows: In the case of an equal variability, the significant difference was calculated by Scheffe's multiple comparison following ANOVA. If an equal variability was absent, statistical analysis was calculated by a Scheffe's type or Dunnett's type multiple comparison (8, 9) following Kruskal-Wallis analysis (10).

RESULTS

Effect of long-term treatment

Preventive effect on hypertension development: Systolic blood pressure of the control group was 112 ± 3 mmHg at 4-weeks old (Fig. 1). It rose linearly with age and reached the level of 200 ± 3 mmHg at 9-weeks old. Thereafter, it rose slowly and reached the plateau level of 209 ± 1 mmHg after 11-weeks of age. Heart rate of the control group was 461 ± 9 beats/min at 4-weeks old. It decreased with age and reached the minimum of 395 ± 9 beats/min at 10-weeks old. After that, however, it slightly increased and remained between 400 and 420 beats/min.

TA-6366 at the dose of 5 mg/kg/day, but not at 1 mg/kg/day, slightly but significantly impeded the hypertension development from 2 weeks after the beginning of treatment and kept the blood pressure 30-40 mmHg lower than that of the control group from 4 weeks after the beginning of treatment to the end. TA-6366 at 1 mg/kg/day did not affect the developing phase of hypertension, but significantly lowered the plateau level of blood pressure by 10 -15 mmHg from the 6th week to the end of treatment.

The rise of blood pressure of the enalapril group proceeded at a similar rate to that in the control group during the first 3 weeks of treatment, but it progressed more slowly during the fourth week. Thereafter, the blood pressure remained almost constant at a lower level than that of the control (P < 0.01), but at a level 5 to 10 mmHg higher than that of the TA-6366 5 mg/kg/day group. The pattern and degree of the change in blood pressure of the captopril group were almost the same as those of the TA-6366, 1 mg/kg/day group.

The heart rate of the TA-6366 1 mg/kg/day group showed almost the same pattern as that
of the control group, whereas the heart rate of the TA-6366, 5 mg/kg/day group was slightly, but not significantly, lower (about 30–40 beats/min) than that of the control group from 5 weeks after the beginning of treatment to the end.

The heart rate of the enalapril group, almost like that of the TA-6366, 5 mg/kg/day group, was slightly, but not significantly, lower (about 20–30 beats/min) than that of the control group from 5 weeks after the beginning of treatment to the end. On the other hand, the heart rate of the captopril group was almost the same as that of the control group.

During the experimental period, no significant difference in body weight increase was observed between the control group and all the drug-treated groups (data not shown).

Effect on urine volume, urinary electrolytes and water intake: TA-6366, like enalapril and
captopril, caused no significant change in the urine volume, Na⁺/K⁺ ratio or water intake (Table 1).

**Effect on heart and kidney weights:** Relative heart weights of both the TA-6366 groups significantly decreased as compared with those of the control group (Table 2). On the other hand, relative heart weight of the enalapril group also decreased to almost the same extent as that of the TA-6366, 1 mg/kg group, but not significantly. In the captopril group, no significant decrease was observed. There was no significant change in the relative kidney weights of any of the drug-treated groups.

**Effect on PRA and plasma AT-I concentration:** In both of the TA-6366 groups, PRA and plasma AT-I concentrations, which were measured at 6 hr after the last treatment, were significantly higher than those of the control group, and their extent of increase depended on the dose (Table 3). These parameters in the enalapril group also increased significantly and those in the captopril group increased slightly.

**ACE activity in the thoracic aorta, lung, brain and serum:** Twenty-four hr after the final dosing, ACE activity of the TA-6366 groups was reduced in the lung, thoracic aorta and brain, whereas that in serum was almost the same as the control level (Fig. 2). In particular, the significant reduction in the aorta was observed in both the 1 and 5 mg/kg/day groups. ACE activity in the lung and aorta of the enalapril group was reduced slightly, but not significantly. The brain ACE activity of the enalapril group was almost the same as that of the control group. In contrast, serum ACE activity significantly rose above the control level. In the captopril group, ACE activity in the lung and aorta slightly, but not signifi-

### Table 1. Urine volume, urinary electrolytes concentration and water intake after 10-weeks oral treatment with TA-6366, enalapril and captopril in SHRs

| Drugs      | Dose (mg/kg/day) | No. of rats | Urine volume (ml) | Na⁺ (μEq/100 g body weight) | K⁺ (μEq/100 g body weight) | Na⁺/K⁺ | Water intake (ml) |
|------------|------------------|-------------|-------------------|-----------------------------|---------------------------|--------|------------------|
| Distilled water | 16.1 ± 2.5      | 7           | 393.9 ± 23.9      | 819.1 ± 31.5               | 0.48 ± 0.01               | 35.4 ± 3.8 |
| TA-6366    | 1                | 8           | 14.0 ± 1.6        | 388.6 ± 23.9               | 792.6 ± 31.6              | 0.49 ± 0.02 | 32.1 ± 2.0 |
| Enalapril  | 5                | 8           | 17.9 ± 4.6        | 423.6 ± 43.1               | 878.3 ± 99.5              | 0.49 ± 0.01 | 36.4 ± 4.6 |
| Captopril  | 5                | 8           | 17.7 ± 2.8        | 420.9 ± 23.6               | 834.4 ± 44.2              | 0.50 ± 0.01 | 38.4 ± 3.6 |

Each value represents the mean ± S.E.M.

### Table 2. Relative heart and kidney weights after 10-weeks oral treatment with TA-6366, enalapril and captopril in SHRs

| Drugs      | Dose (mg/kg/day) | No. of rats | Weights (mg/100 g body weight) |
|------------|------------------|-------------|--------------------------------|
|            |                  |             | heart                          |
| Distilled water | 9                | 339 ± 3.9   | 346 ± 4.2                      |
| TA-6366    | 1                | 9           | 308 ± 5.1                      | 340 ± 4.3                   |
|            | 5                | 9           | 300 ± 3.0                      | 354 ± 8.0                   |
| Enalapril  | 5                | 8           | 310 ± 2.9                      | 352 ± 9.2                   |
| Captopril  | 5                | 8           | 345 ± 14.1                     | 344 ± 5.5                   |

Each value represents the mean ± S.E.M. Significantly different from the control: *P < 0.05, **P < 0.01 (Scheffe type multiple comparison).
significantly, rose above the control level, whereas that in the brain was about the same level as the control. In addition, ACE activity in serum significantly rose to about 2 times the control value.

Changes of blood pressure and ACE activity after withdrawal

Following cessation after 9-weeks treatment with TA-6366 at 5 mg/kg/day, blood pressure rose gradually, but it remained significantly lower as compared with that of the control group for at least 10 weeks (Fig. 3).

Nine days after withdrawal, ACE activity in the aorta of both the TA-6366 groups was still at the reduced level, the decrease being dose-dependent (Fig. 4), whereas that in the other tissues almost returned to the control levels.

### Table 3. Plasma renin activity (PRA) and plasma angiotensin I (AT-I) concentration 6 hr after 10-weeks oral treatment with TA-6366, enalapril and captopril in SHRs

| Drugs          | Dose (mg/kg/day) | No. of rats | PRA (ng/ml/hr) | AT-I (mg/ml) |
|----------------|------------------|-------------|----------------|--------------|
| Distilled water| 7                | 10.24 ± 1.17| 2.09 ± 0.15    |
| TA-6366        | 1                | 55.24 ± 9.25** | 8.28 ± 1.42*   |
|                | 5                | 80.56 ± 5.47** | 17.63 ± 2.20** |
| Enalapril      | 5                | 63.04 ± 8.24** | 10.38 ± 1.92** |
| Captopril      | 5                | 28.96 ± 4.44 | 4.26 ± 0.48    |

Each value represents the mean ± S.E.M. Significantly different from the control: *P < 0.05, **P < 0.01 (Dunnett type multiple comparison).

Fig. 2. Angiotensin I converting enzyme (ACE) activity in serum and tissue of SHRs 24 hr after 10-weeks oral treatment with TA-6366, enalapril and captopril. Each column indicates the mean ± S.E.M. N = 7-8. 

□: distilled water (10 ml/kg); ■: TA-6366, 1 mg/kg/day, p.o.; □: TA-6366, 5 mg/kg/day, p.o.; ■: enalapril, 5 mg/kg/day, p.o.; □: captopril, 5 mg/kg/day, p.o. Significantly different from the distilled water-treated group: *P < 0.05, **P < 0.01.
Fig. 3. Changes in systolic blood pressure after withdrawal of 9-weeks treatment with TA-6366. Each point represents the mean ± S.E.M. N = 8. Some of the standard errors are within the symbols. ○: distilled water (10 ml/kg); △: TA-6366, 5 mg/kg/day, p.o. Significantly different from the distilled water-treated group: *P < 0.05, **P < 0.01.

Fig. 4. Angiotensin I converting enzyme (ACE) activity in serum and tissue of SHRs 9 days after 10-weeks oral treatment with TA-6366, enalapril and captopril. Each column indicates the mean ± S.E.M. N = 6-7. □: distilled water (10 ml/kg); △: TA-6366, 1 mg/kg/day, p.o.; ○: TA-6366, 5 mg/kg/day, p.o.; ◯: enalapril, 5 mg/kg/day, p.o.; ■: captopril, 5 mg/kg/day, p.o. Significantly different from the distilled water-treated group: *P < 0.05, **P < 0.01.
In particular, the aortic ACE activity of the 5 mg/kg/day group was almost the same level as that obtained at 24 hr after the final dosing. In the enalapril group, ACE activity in the lung, aorta and serum almost returned to the control level, whereas that in the brain rose slightly. ACE activity in the lung and serum of the captopril group almost returned to the control level, whereas that in the aorta and brain slightly rose.

DISCUSSION

The long-term oral administration of TA-6366 (5 mg/kg/day) from 4-weeks old when the hypertension development is not yet initiated, impeded the genetic hypertension development in SHRs. Enalapril also impeded the development even at the much lower dose than that in the earlier report (2), although the effect was observed 2 weeks later than that of TA-6366. In addition, TA-6366 at the lower dose (1 mg/kg/day) did not affect the development, but it lowered blood pressure after the development was almost accomplished.

Recent techniques in molecular biology have revealed that both renin and angiotensinogen genes are expressed in tissues such as blood vessels, heart, kidney, brain and adrenal gland (11, 12). In particular, as to the vascular renin-angiotensin-system (RAS), it has been reported that renin and ACE activities are elevated in the aorta of both young and adult SHRs relative to those of age-matched WKY rats (13–17). These reports are thought to strongly support the contribution of the vascular RAS to the hypertension mechanism of SHRs. In this study, ACE activity in the aorta was reduced more potently and persistently than those in the lung, brain and serum 24 hr and 9 days after the final dosing of TA-6366 at both 1 and 5 mg/kg/day. The present result suggests that AT-II biosynthesis in the vasculature may be suppressed persistently during the period of treatment with TA-6366. Therefore, the beneficial effects of TA-6366 on the hypertension development and the following hypertension seem to be related to the suppression of AT-II biosynthesis in the vasculature resulting from its ACE inhibitory action.

As to enalapril and captopril, however, we could not clarify whether reduction in blood pressure relates to the inhibition of ACE activity in the vasculature. Persistent reduction in ACE activity of the aorta could not be found in the both enalapril and captopril groups after withdrawal. As the principal cause of this, there are the following two possibilities. The first possibility is that the durations of ACE inhibitory action of these drugs are shorter than that of TA-6366. Supporting this possibility is the fact that serum ACE activity in both these groups treated with enalapril and captopril significantly rose above the control level, and the aortic ACE activity also tended to increase in the latter group. The second possibility is that the biosynthesis of ACE in the aorta may be accelerated through the feedback mechanism. As to the elevation of intrinsic ACE activity, it has been already reported that enalapril and captopril increase the ACE activity in the lung and serum after they were administered repeatedly (18–21), supporting this possibility.

The relative heart weight was decreased in both the TA-6366 groups and the enalapril group, as compared with those in the control group, but not in the captopril group. It has been already shown that ACE inhibitors, including enalapril, cause regression of cardiac hypertrophy (22–24). Recently, AT-II has been reported to have growth promoting action in cultured vascular and cardiac myocytes (25, 26). Thus, the mechanism of the heart weight-reducing action of TA-6366 might be related to the inhibition of AT-II-dependent myocardial protein synthesis due to its ACE inhibitory action in addition to the reduced cardiac afterload that is seen as a consequence of blood pressure reduction. The difference in the potencies on heart weight among TA-6366, enalapril and captopril may correlate with the potency and duration of their ACE inhibitory action in the vasculature, heart and serum.

After withdrawal of TA-6366, the lowered
blood pressure persisted over a long period. We observed that long-term treatment with TA-6366 starting at 4-weeks old, decreased both the wet and dry weights in the thoracic aorta of SHRs (M. Kubo et al., unpublished data). Considering that AT-II is not only a vasopressor substance but one of the cell growth factors (26), the decrement of aorta weight seems to be partly related to the reduction of AT-II biosynthesis in the vasculature through the ACE inhibitory action of TA-6366. Therefore, it suggests that the persistently lowered blood pressure may result from a protective effect of TA-6366 against progression of structural vascular abnormalities such as vascular hypertrophy contributory to the maintenance of elevated peripheral vascular resistance in SHRs. However, to discuss whether such a sustained fall in blood pressure after withdrawal of TA-6366 closely correlates to its long-lasting ACE inhibition in the vasculature, further experiments are needed.

TA-6366 showed no significant changes in heart rate, body weight gain, urine volume, urinary electrolyte contents or water intake, suggesting that long-term treatment with TA-6366 causes no adverse reactions, such as tachycardia, body fluid volume expansion or dipsosis.

TA-6366, like enalapril and captopril, increased PRA and plasma AT-I concentration. Renin release from the kidney is generally well known to be enhanced because of the compensatory mechanism due to reduction of the circulating AT-II concentration. In addition, the increment of plasma AT-I concentration seems to be attributable to the inhibitory action of TA-6366 on both the circulating and lung ACE. Thus, the result suggests the reduction of the circulating AT-II concentration. However, its reduction may not be attributable to the preventive action of TA-6366 on hypertension development in SHRs, because PRA of SHRs is normal or lower (27–29).

In conclusion, long-term treatment with TA-6366 prevented genetic hypertension development and decreased the relative heart weight in SHRs without simultaneously inducing tachycardia and body fluid volume expansion. The beneficial effect of TA-6366 on hypertension development seems to be related to its persistent ACE inhibition in the vasculature.

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