Angiotensin II receptor blocker-induces blunted taste sensitivity: comparison of candesartan and valsartan

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Aims

To compare the degree of taste disturbance by candesartan and valsartan.

Methods

Candesartan cilexetil (4 mg day⁻¹), valsartan (40 mg day⁻¹), or vehicle was given to subjects ($n = 8$) for 13 days in a randomized, placebo-controlled, three-way crossover design with a 14-days washout period. Gustometry by filter-paper test and electrogustometry were performed before and at the end of each trial. Plasma renin activity and zinc concentrations in serum and saliva were measured.

Results

Detection thresholds of four basic tastes (sweet, salty, sour and bitter) by paper-disc test and electrogustometry were significantly worsened and plasma renin activity was elevated after the test, while the effects of two drugs did not significantly differ. These drugs did not affect zinc concentrations.

Conclusion

Both candesartan and valsartan similarly alter taste sensitivity after the repeated dosing of the drug.

Introduction

Taste disturbance is caused by several endogenous and exogenous factors, about 20% of which are drug-related including antihypertensive drugs [1, 2]. Angiotensin converting enzyme inhibitors are well known to cause the taste disturbances by either serum zinc concentration-dependent or -independent mechanisms [2–4]. However, information for angiotensin II receptor blocker (ARB) is limited. There are three case reports about ARB-induced taste disturbance (losartan [5, 6] and valsartan [7]). We have recently showed that the

taste sensitivity was subclinically disturbed by candesartan, another ARB, in healthy subjects [8]. These findings indicate that this effect might be a class effect of ARB. However, this hypothesis is not proven, because ARB-induced taste disturbance was prospectively detected only for candesartan by our previous report, but not for other ARBs. To prove this, we need to evaluate the effect on taste of several other ARBs. In such a case, comparison with candesartan as well as placebo is preferable. In this study, we compared the effect of the repeated oral dosing of two different ARBs, candesartan

and valsartan, on taste sensitivity by a randomized, double-blind, placebo-controlled, crossover study in healthy subjects.

Methods

Eight healthy nonsmoking men (29–47 years) were enrolled in this study. All subjects gave written informed consent. The study design was a randomized, double-blind, placebo-controlled, three-way crossover design with a 2-week washout period. On Day 1 (observation period), the detection thresholds for tastes were determined and salivary fluid was obtained at 09.00 h, 12.00 h, 15.00 h and 21.00 h. Subjects took candesartan cilexetil (Blopess®, Takeda Pharmaceutical Co. Ltd, Tokyo, Japan, 4 mg), valsartan (Diovan®, Novartis, Pharma Co. Ltd, Tokyo, Japan, 40 mg) or placebo (100 mg of lactose) at 09.00 h from Day 2 to Day 14. On Day 14, the evaluation test and samplings of salivary fluid and blood were performed at 09.00 h, 12.00 h, 15.00 h and 21.00 h. On the day of taste evaluation, a similar light meal (sandwich with milk) was served for lunch to all subjects at 15.00 h. Subjects were prohibited from taking any other food or drink until the end of the test. Blood pressure at 24 h before final dosing of the drug was measured in each subject. After the washout period for 2 weeks, an identical protocol was repeated in a crossover fashion. The protocol was approved by the Ethical Committee of Jichi Medical School.

Two types of gustometries were performed in each subject [8]. (1) Semi-quantitative clinical gustometry using filter-paper discs (the filter-paper disc method: Taste disc®, Sanwa Chemical Laboratory, Nagoya, Japan) which is routinely used for the evaluation of dysgeusia in the clinical setting [9–11]. In brief, recognition thresholds for four basic tastes (sweet, salty, sour and bitter) were evaluated using the chemical solutions (sucrose, NaCl, tartaric acid and quinine, respectively). The solutions were sequentially diluted with distilled water into five grades (1 is the lowest). A droplet of each solution was added to filter paper, placed on the left side of the tongue 2 cm from the tip (i.e. locus for left chorda tympani nerve). Subjects selected a single answer from the following list: sweet, salty, sour, bitter, unidentifiable taste, or no taste. (2) Electrogustometer, as routinely used for the evaluation of hypogeusia in oto-rhino-laryngology clinic, performed according to the method of Tomita *et al.* [9, 10, 12] using commercially available equipment (TR-06®, Rion Co., Ltd, Tokyo, Japan). In brief, a single type stimulation rod was placed on the left side of the tongue 2 cm from the tip. The smallest stimulus that the subjects noticed was regarded as the

detection threshold. Normal range was less than +14 dB [9, 10, 12].

Spontaneously salivated salivary fluid was collected into a special polyethylene tube after gargling with distilled water three times [8]. Blood samples were taken from the cubital vein. Both salivary fluid and serum/plasma were stored at -80°C until the assay. Total zinc concentration was measured by atomic absorption spectrophotometry [13]. Plasma renin activity was measured by radio-immunoassay [14].

All data are expressed as the mean $\pm$ SE. Statistical analysis was performed by ANOVA using StatView 5 for Windows (SAS Institute Inc, NC). $P < 0.05$ was regarded as significant.

Results

All subjects completed the protocol without any complaints of taste disturbance. Mean blood pressure just before final dosing of the drug was not different between the three trials (110.5 ± 2.3 , 108.1 ± 2.7 and 107.6 ± 2.5 mmHg, placebo, candesartan and valsartan, respectively). Figure 1 shows the recognition thresholds for sweetness using filter-paper disc at the end of the repeated treatment. It was significantly ($P < 0.05$) worsened after the repeated treatment of candesartan or valsartan, but not after placebo. The mean $\pm$ SE (and 95% CI) scores for the sweetness just before the 13th dosing

Figure 1

Detection thresholds for sweetness using filter-disc after the repeated dosing of candesartan, valsartan and placebo. Four basic tastes (sweet, salty, sour and bitter) were evaluated by using chemical solutions at the end of each treatment (day 14 + day 42 + day 70). A similar test was performed just before each protocol (day 1 + day 29 + day 57) and it was confirmed that the disturbances were completely improved after the washout period (data not shown). Mean $\pm$ SE, $n = 8$, Candesartan (○), Valsartan (□), Placebo (●)

Table 1

Difference of area under the time-score curve of tests, and time-concentration curve of zinc and plasma renin activity between drug and placebo

	Candesartan	Valsartan	95% CI
Sweet (U h ⁻¹)	15.75 ± 2.71	10.69 ± 2.43	(-6.15 to 16.27)
Salty (U h ⁻¹)	22.88 ± 5.16	19.75 ± 4.10	(-22.94 to 31.39)
Sour (U h ⁻¹)	11.06 ± 3.23	8.44 ± 2.69	(-11.74 to 16.99)
Bitter (U h ⁻¹)	12.94 ± 3.41	9.56 ± 2.39	(-12.43 to 19.68)
Electrogustometer (dB h ⁻¹)	42.98 ± 10.25	22.82 ± 11.41	(-10.67 to 50.93)
Salivary Zinc (mg dl ⁻¹ h ⁻¹)	-14.7 ± 10.8	-18.8 ± 14.5	(-10.2 to 8.9)
Serum Zinc (mg dl ⁻¹ h ⁻¹)	-18.9 ± 20.2	-37.3 ± 33.5	(-24.2 to 15.5)
Plasma renin activity (ng ml ⁻¹)	182.1 ± 25.7	228.9 ± 34.2	(-18.5 to 50.7)

was 3.75 ± 0.25 (3.48–4.15), 3.53 ± 0.23 (3.19–3.94) and 2.13 ± 0.30 (1.75–2.55), for candesartan, valsartan and placebo, respectively. The detection thresholds of other three tastes were also significantly ($P < 0.05$) worsened after the repeated treatment of candesartan or valsartan, but not after placebo (data not shown). Difference of area under the time-score curve (determined by trapezoidal method) between a drug and placebo was shown in Table 1. The decrements of parameters were not different between candesartan and valsartan. The thresholds of the tastes just before each treatment were not different between the three groups (data not shown).

Detection thresholds at the end of each repeated treatment using an electrogustometer was also worsened by candesartan or valsartan to the same extent, but not by placebo (data not shown). Differences of area under the time-score curve (determined by trapezoidal method) between the drugs and placebo are shown in Table 1. The thresholds before each trial were not significantly different between the three groups (data not shown).

Salivary and serum zinc concentrations and plasma renin activity at the end of the repeated treatment were measured. Differences of area under the time-concentration curve (determined by trapezoidal method) between the drugs and placebo were shown in Table 1. Serum zinc concentration at 12 h after final dosing was significantly lower than other points in each trial. Plasma renin activity at the end of the repeated treatment was significantly higher in the trial with candesartan and valsartan than with placebo. However, no significant differences between the drug-treated groups were observed in these parameters.

Discussion

We measured plasma renin activity just before the taste test in this study because ARBs enhance plasma renin

activity by the negative feedback after blocking angiotensin II receptor [15]. We found that both candesartan and valsartan at the doses used in this study (4 and 40 mg, respectively) increased this variable to a similar extent, which indicated that the treatment with candesartan and valsartan affected systemic renin-angiotensin-aldosterone axis to a similar degree. It is reported that 8 mg of candesartan and 80 mg of valsartan were equivalent to increment of plasma renin activity in healthy subjects [15], which is comparable to our study.

We compared two different ARBs on taste sensitivity in healthy subjects and found that the repeated oral dosing of candesartan and valsartan blunted taste sensitivity to a similar extent. To evaluate taste sensitivity, we used the same tests as our recent report [8] with a longer period of treatment from 7 to 13 days in this study. In addition, we found that the changes of the taste after the test were comparable for candesartan. Therefore, the alteration of taste reached a plateau in the earlier period of the treatment. In case reports of ARB-induced taste disturbance, patients noticed the problem from 1 week to 3 months after the initiation of the treatment with losartan [5, 6] and valsartan [7]. Based on our data and previous case reports, the taste disturbance might occur within a week, but patients needed several weeks to notice it.

We also measured serum zinc concentration because captopril disturbed taste sensitivity by chelating zinc in the body [3]. We found that both candesartan and valsartan did not change zinc concentration in serum and saliva, which is similar to our previous study using candesartan.

The mechanism of ARB-induced taste disturbance is not clear at the present time. Receptors for salt and sour in taste cell are elicited by ion channels [17] and may be affected by extra-cellular ion composition. Interest-

ingly, Lundy *et al.* proposed possible interaction of Na ion with the receptors [18]. Although we did not measure this parameter in serum and saliva, serum Na concentration is reduced by ARBs during the treatment in clinical situation [19]. It is uncertain that nerve conduction is disturbed. Further study is needed to solve this issue.

In summary, this study shows that the repeated dosing of candesartan and valsartan subclinically reduces the sensitivity of basic tastes in healthy subjects. The taste sensitivity was altered and plasma renin activity was elevated to the similar extent by both drugs. These results suggest that the taste disturbance-induced by candesartan is potentially similar to that of valsartan.

Competing interests: None declared.

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