Aims Stevioside is a natural plant glycoside isolated from the plant Stevia rebaudiana which has been commercialized as a sweetener in Japan for more than 20 years. Previous animal studies have shown that stevioside has an antihypertensive effect. This study was designed to evaluate the effect of stevioside in human hypertension.

Methods A multicentre, randomized, double-blind, placebo-controlled study was undertaken. This study group consisted of 106 Chinese hypertensive subjects with diastolic blood pressure between 95 and 110 mmHg and ages ranging from 28 to 75 years with 60 subjects (men 34, women 26; mean ± s.d., 54.1 ± 3.8 years) allocated to active treatment and 46 (men 19, women 27; mean ± s.d., 53.7 ± 4.1 years) to placebo treatment. Each subject was given capsules containing stevioside (250 mg) or placebo thrice daily and followed-up at monthly intervals for 1 year.

Results After 3 months, the systolic and diastolic blood pressure of the stevioside group decreased significantly (systolic: 166.0 ± 9.4–152.6 ± 6.8 mmHg; diastolic: 104.7 ± 5.2–90.3 ± 3.6 mmHg, P<0.05), and the effect persisted during the whole year. Blood biochemistry parameters including lipid and glucose showed no significant changes. No significant adverse effect was observed and quality of life assessment showed no deterioration.

Conclusions This study shows that oral stevioside is a well tolerated and effective modality that may be considered as an alternative or supplementary therapy for patients with hypertension.

Keywords: compliance, hypertension, stevioside

Introduction
Hypertension is an important risk factor for cardiovascular mortality and morbidity in epidemiological studies [1, 2]. Improvements in identification and treatment of hypertension have contributed to a major reduction in the incidence of cardiovascular disease in many countries [3, 4]. Despite these major advancements in detection and pharmacological treatment of hypertension, inadequate blood pressure control persists as a major public health problem [5]. Compliance of patients to antihypertensive therapy may be an important barrier to optimal blood pressure control as some antihypertensive drug treatment may have a negative impact on the quality of life [6, 7]. If a new antihypertensive agent is developed with good efficacy and tolerability and, which could also be used as a health food supplement, it could have a significant clinical benefit in the control of hypertension.

Stevioside is a glycoside isolated from the plant Stevia rebaudiana Bertoni, which has been widely used as a sweetening agent in Japan for 20 years [8, 9]. In pure form, stevioside is a white crystalline material with a melting point of 196–198°C, an optical rotation of −39.3° in water, and an elemental composition of C38H60O18 (Figure 1). There are a few reports concerning the effects of stevioside and other natural products from S. rebaudiana on the cardiovascular system. Previous investigators have shown that purified stevioside induces
Recent studies from our laboratory have shown that intravenous administration of stevioside resulted in a significant hypotensive effect in spontaneously hypertensive rats without adverse effects on heart rate or serum catecholamine levels [11]. Since stevioside has been used as a natural sweetener for 20 years, and no significant adverse effects have been reported, this helps to establish its safety in long-term human usage. This study was undertaken to evaluate the tolerabilities and efficacy of stevioside glycoside in the treatment of human hypertension.

**Methods**

This was a multicentre, randomised, double-blind, placebo-controlled study. The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki and was approved by the investigation review board of each participating centre. All patients gave written informed consent.

**Patient population**

Patients of both sexes (20–75 years) with a previous diagnosis of mild to moderate essential hypertension were enrolled for the study. The patients had to be otherwise apparently healthy and free of secondary causes of hypertension, other cardiac disease, malignancies, significant renal impairment (serum creatinine > 2.0 mg dl\(^{-1}\)) or hepatic dysfunction.

**Conduct of study**

After providing informed consent, and the withdrawal of any previous antihypertensive treatment, eligible patients entered a 4 week, single-blind, placebo wash-out phase. Those whose sitting diastolic blood pressure was between 95 mmHg and 115 mmHg (average of three readings as described below) at the last two visits of the placebo period were eligible for randomization. Patients were requested to attend for follow-up every 2 weeks during placebo washout and during active treatment phases to assess side-effects and measure blood pressure. Treatment group patients were given stevioside (Nan Kai Chemical Factory, Tien Jing, China) capsules 250 mg thrice a day and the control group were given matching placebo. They also underwent complete physical examination (including fundoscopy), chest radiography, 12-lead electrocardiogram and laboratory tests (biochemistry, haematology and urinalysis). Blood pressure was measured by trained personnel who were experienced in measuring blood pressure for epidemiological surveys. Blood pressure was measured to the nearest 2 mmHg, using a standard mercury sphygmomanometer, after the subject had been sitting for 10 min rest. Korotkoff phases I and V were taken as the systolic and diastolic blood pressures, respectively. The blood pressure was measured consecutively three times at 5 min intervals and a 30 s pulse recording made at each measurement. The mean of the three measurements was used for the analysis. Diet counselling was carried out by a registered dietician.

Efficacy assessment was based on the mean change from baseline in the sitting systolic and diastolic blood pressures at the end of 1 year of double-blind treatment. The modified Vital Signs Quality of Life Questionnaire was used to assess the impact of treatment on quality of life [12]. The questionnaire was administered before double-blind treatment was commenced and at each subsequent visit. This questionnaire contains a 25-question survey which assesses overall satisfaction with study drug treatment, as well as the frequency and intensity of problems associated with general health, relationships with others, mental functioning, and emotional state.

**Clinical evaluation and blood sampling**

Demographic data, including age, sex, and body mass index (kg/m\(^2\)), were recorded at the initial visit and weight recorded at each follow-up visit. Venous blood was drawn at 08.00 h and 10.00 h after subjects had fasted overnight. The participants were asked to abstain from heavy meals for 48 h before their visit. Blood was collected into suitable tubes for determination of insulin, glucose, lipids, renal function, electrolytes, and transaminases. Glucose, cholesterol, triglycerides, uric acid, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, and creatinine levels were measured with a Monarch Autoanalyser System (Instrumentation Laboratories, Tx, USA).
Total cholesterol and triglycerides were measured enzymatically with commercially available kits (Boehringer Mannheim, Mannheim, Germany). HDL-C level was obtained after precipitation, and another lipoprotein LDL-C was calculated by the Friedewald approximation.

**Clinical safety and compliance**

A complete physical examination, including a chest roentgenogram and 12-lead electrocardiogram, was carried out before administration of active medication and at the end of the study. Clinical laboratory tests, including complete blood counts with differential leucocyte counts and microscopic and dipstick urinalyses, were also done at each visit.

All clinical adverse events, either volunteered or elicited by questioning, at baseline and follow-up visits were recorded. Compliance was evaluated by tablet counting.

**Statistics**

Statistical analysis were carried out with the Statistical Analysis System, version 6.06 (SAS Institute Inc, NC, USA). Dispersion of data is given by mean ± s.d. When within group data were compared, the Wilcoxon Signed Ranks was used. When comparison between groups was made Mann-Whitney test was used. The incidence of adverse effects and laboratory abnormalities in the two treatment groups was determined with Fisher’s exact test.

**Results**

**Baseline characteristics with the study population**

The 106 randomized Chinese subjects (53 women, 53 men) had a mean age of 54 years, with a mean body mass index of 23.4 kg m$^{-2}$. Mean systolic BP was 160 mmHg, and diastolic BP was 102 mmHg. At the beginning of randomization, both placebo and active treatment groups were similar in demographic, clinical and biochemical characteristics (Table 1). During the placebo wash-out phase, systolic and diastolic BP did not fall significantly in either group. Body weight and other biochemical parameters did not change significantly in either group during this study.

**Efficacy of stevioside**

The baseline and endpoint BP results are summarized in Table 1. The BP levels in the placebo and active treatment groups were not different at baseline but after three months. Both systolic and diastolic BP of the active treatment group were significantly different from placebo. The reduction in BP (data not shown) began from 7 days by patients self-monitoring record and persisted throughout the whole treatment period (Figure 2). The mean reduction in systolic BP was 12 mmHg and diastolic BP was 8 mmHg (Table 1).

**Tolerability and compliance with stevioside**

The drug was well tolerated. Only six patients (two from the placebo group, four from the stevioside group) were withdrawn before the last scheduled study visit for the following reasons: lost to follow-up (two patients), and side-effects (four patients, three from active treatment group, one from placebo group) (Table 2). At the outset, four more patients from the active treatment group experienced abdominal fullness, muscle tenderness, nausea and asthenia, but all of the symptoms disappeared after continued intake of drug for 1 week. Laboratory tests, either at baseline or during double-blind treatment, showed no significant difference between the two groups. All the remaining subjects followed the prescribed treatment schedule during the entire 12 month treatment period. Subjects’ compliance was evaluated by tablet counting, which showed a similar degree of compliance in the two treatment groups throughout the entire course of randomized treatment. Tablet intake averaged 95 ± 4% of the planned number of tablets of placebo group at randomization and 92 ± 3% during double-blind treatment in the placebo group. The stevioside group intake averaged 96 ± 3% at randomization and 93 ± 3% during double-blind treatment. There were no cardiovascular events in either group during the study.

**Quality of life**

Quality of life scores were maintained during the weeks of double-blind treatment. No statistically significant differences were found between pre- and post-treatment scores for any of the treatments when analysing the results of the quality of life questionnaire, nor were there differences between treatment groups. The percentage of patients reporting improvement in quality of life was also evaluated comparing pre- and post-treatment. Again, no significant differences were found between the two groups, although all the active treatment groups tended to improve more than the placebo group (58% vs 52%).

**Discussion**

Hypertension is a chronic, asymptomatic condition requiring continuous treatment to maintain blood pressure under good control. The achievement of goal blood pressure requires high compliance with appointment-keeping, medication intake, and often life style modifications which may be difficult to sustain in the long term.
Consequently only about 20% of all hypertensive patients are under appropriate medical treatment with goal blood pressure achieved [5].

In the past 20 years the health-care professional community has become increasingly aware of the importance of compliance as a factor in the successful treatment of health problems. For a variety of reasons, hypertension has served as a model for the understanding of compliance [13]. A major reason for the prominent role of hypertension in compliance research is that low compliance remains an important cause for poor blood pressure control [14]. One major adverse drug effect that impairs adherence to therapy is sexual dysfunction [15–20]. Additionally, the assumption that impairment of sexual function will result from antihypertensive drug treatment may inhibit a large group of patients from seeking appropriate antihypertensive therapy [21]. The present data show that stevioside is not only an effective drug for lowering blood pressure, but that it also has no adverse effect on sexual function since our questionnaire included assessment of sexual function.

Table 1 Baseline and end-point demographic and fasting biochemical data of placebo and stevioside group.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>Stevioside</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End-point</td>
<td>Baseline</td>
<td>End-point</td>
</tr>
<tr>
<td>n, men/women</td>
<td>19/27</td>
<td>18/26</td>
<td>34/26</td>
<td>32/24</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>23.6 ± 2.8</td>
<td>23.4 ± 2.6</td>
<td>23.2 ± 2.5</td>
<td>23.3 ± 2.4</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>166.0 ± 9.4</td>
<td>164.8 ± 8.7</td>
<td>166.5 ± 7.4</td>
<td>152.6 ± 6.8*</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>104.7 ± 5.2</td>
<td>103.8 ± 5.4</td>
<td>102.1 ± 4.0</td>
<td>90.3 ± 3.6*</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>68.2 ± 7.8</td>
<td>69.4 ± 8.1</td>
<td>66.4 ± 7.2</td>
<td>67.4 ± 6.8</td>
</tr>
</tbody>
</table>

**Serum values**
- Creatinine (µmol l⁻¹) 106.1 ± 26.5 97.2 ± 17.7 114.9 ± 26.5 106.1 ± 17.7
- CPK (U l⁻¹) 50 ± 18 49 ± 20 52 ± 17 49 ± 19
- AST (U l⁻¹) 16 ± 4 18 ± 7 15 ± 5 18 ± 9
- ALT (U l⁻¹) 20 ± 5 19 ± 6 21 ± 5 17 ± 6
- Na (mmol l⁻¹) 142.8 ± 6.0 140.8 ± 3.2 141.5 ± 5.1 140.2 ± 4.3
- K (mmol l⁻¹) 4.2 ± 0.4 4.5 ± 0.4 4.4 ± 0.4 4.4 ± 0.5
- Cl (mmol l⁻¹) 100.4 ± 14.8 100.9 ± 15.0 99.8 ± 3.5 98.3 ± 2.0

**Plasma values**
- Glucose (mmol l⁻¹) 5.6 ± 0.8 5.4 ± 0.5 5.5 ± 0.7 5.3 ± 0.7
- Total cholesterol (mmol l⁻¹) 4.7 ± 1.0 5.1 ± 0.9 5.2 ± 1.0 5.1 ± 1.2
- HDL-C (mmol l⁻¹) 1.1 ± 0.1 1.1 ± 0.1 1.1 ± 0.1 1.1 ± 0.1
- Triglycerides (mmol l⁻¹) 1.7 ± 0.9 1.7 ± 0.6 1.7 ± 0.6 1.7 ± 0.6

BMI indicates body mass index; CPK, creatinine phosphokinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Na, sodium; K, potassium; and Cl, chloride. No significant difference was noted between placebo and stevioside groups at baseline. Values are mean ± s.d. End-point vs baseline in each group. *P<0.05.

Figure 2 The serial changes in systolic and diastolic blood pressure in patients receiving stevioside 250 mg thrice daily or placebo for 12 months.

Table 2 Side-effect of subjects taking placebo or stevioside.

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Placebo (n = 46)</th>
<th>Stevioside (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2(1*)</td>
</tr>
<tr>
<td>Abdominal fullness</td>
<td>1</td>
<td>2(1*)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>1(1*)</td>
</tr>
</tbody>
</table>

*Sufficient to stop treatment.
and requirement for multiple medications [24]. Generally, hypertension treatment is a long-term proposition necessitating daily administration of medication to maintain blood pressure under good control. The aim is to minimize the adverse impact of the duration of treatment regimen and to avoid any adverse effects on the patient’s quality of life [25].

The complexity of the medication regimen is also a major determinant of compliance. The compliance rate decreases as the number of daily medications prescribed increases. Previous investigators have found that compliance with antihypertensive medications improved from 59% on a three times daily dose regimen to 86% on a single daily dose regimen, and that compliance with once and twice daily dose regimen was not significantly different [26]. In our previous animal experiments, we found that the duration of action of stevioside was short [11], so we decided to administer the stevioside capsules to patients three times daily. In the Chinese population, the usage of alternative and complimentary or traditional medicine is still very common, and the adherence to traditional medicines is usually better. Since stevioside is a glycoside purified from a plant, patients usually regarded it as a traditional medicine and their compliance was more than 90%.

The tolerability of stevioside appears satisfactory in this study as only a few patients reported minor side-effects, such as dizziness or nausea after taking these capsules and adverse effects reported from the placebo group were similar. Although the hypertensive effect of stevioside was not better than other antihypertensive drugs, it appears comparable and almost all the active treatment group patients showed significant lowering of blood pressure. One interesting phenomenon observed in this study was that the blood pressure began to decrease at about 7 days after taking stevioside capsules. Although the mechanism underlying the antihypertensive effect of stevioside is not fully clear, it has been demonstrated that the hypertensive response to stevioside appears to occur through a calcium antagonist mechanism similar to that of verapamil [27, 28]. However, other studies have shown that the blood pressure lowering effect of stevioside probably depends on prostaglandin activity [8, 9].

In conclusion, stevioside was found to be a safe and effective compound in the treatment of hypertension although the amplitude of blood pressure lowering was slightly less than other antihypertensive drugs. It could therefore be used as a supplementary therapy since it has already been used as a taste-modifying agent for more than two decades.

References


