Symposium

Effect of Long-Acting Isosorbide-5-Mononitrate Administration on Large Artery Distensibility in Patients with Essential Hypertension

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To evaluate the clinical efficacy of long-acting nitrates, isosorbide-5-mononitrate (IS-5-MN), on large artery distensibility in patients with essential hypertension. Large arterial distensibility was assessed by automatic noninvasive measurement of the carotid-femoral pulse wave velocity (PWV). Seventeen patients aged 62.53 ± 7.94 years (mean $\pm$ SD) with essential hypertension under long-term antihypertensive therapy were studied in this trial. PWV was measured 2 weeks and 4 weeks after oral administration of IS-5-MN (30 mg once daily) with previous therapy. There was no significant difference in systolic blood pressure, diastolic blood pressure, pulse pressure or heart rate at 2 weeks and 4 weeks after treatment compared with baseline. The carotid-femoral PWV decreased significantly at 2 and 4 weeks after treatment ($p < 0.05$, $p < 0.05$, respectively). Long-acting nitrates have potential value in improving large arterial distensibility in patients with essential hypertension independent of blood pressure alteration. It might be used as an effectively additive drug in hypertension control. (*Hypertens Res* 2001; 24: 311-314)

Key Words: carotid-femoral pulse wave velocity, arterial distensibility, isosorbide-5-mononitrate

Introduction

Epidemiological studies have shown that reduction in large artery distensibility is a prognostic factor in the development of cardiovascular complications in hypertensive patients (1-5). Advancing age and hypertension contribute independently to increased arterial rigidity, decreased compliance, and impairment in the characteristic buffering function of conduit arteries (5). This results in an earlier and more pronounced reflection of the arterial pulse wave, a disproportionate increase in the central systolic blood pressure, and a relative or absolute decrease in the diastolic blood pressure. These effects, in turn, lead to an increase in pulse pressure, which has been suggested to be an independent cardiovascular risk factor for various complications in hypertensive subjects, particular-

ly myocardial infarction (5).

The increased arterial rigidity can be improved by antihypertensive drugs, especially nitrates, calcium antagonists and ACE inhibitors (6). Vasodilating drugs are widely used in clinical practice and represent a group of agents that have effects on blood pressure, systemic vascular resistance, and vascular compliance. It has also been shown that nitroglycerin infusion increases forearm arterial distensibility, in fact, nitrates were shown to decrease central artery pressure rather than peripheral brachial pressure, and thereby to decrease left ventricle afterload (7).

Because of their short effective duration and drug resistance, nitrates have not been widely used in the field of hypertension treatment. To overcome these drawbacks, a long-acting, slow-released nitrate tablet, IS-5-MN, has recently been developed. The purpose of this pilot study was to investigate the effect of long-acting IS-5-MN on

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Table 1. Patients' Data

	Baseline	2 Weeks therapy	4 Weeks therapy
BMI (kg/m ²)	25.81 ± 3.07	25.79 ± 3.14	25.71 ± 3.11
HR (beats/min)	77.76 ± 11.93	78.00 ± 12.88	77.06 ± 9.80
SBP (mmHg)	145.53 ± 14.32	138.35 ± 14.35	138.41 ± 16.26
DBP (mmHg)	84.82 ± 9.47	80.18 ± 9.01	80.53 ± 9.23
MBP (mmHg)	105.06 ± 9.79	99.57 ± 9.64	99.82 ± 9.93
PP (mmHg)	60.71 ± 12.05	58.18 ± 11.58	57.88 ± 14.43
PWV (m/s)	12.59 ± 2.24	10.90 ± 1.69*	10.99 ± 1.81*

Data are presented as the means ± SD. BMI, body mass index, calculated from body weight divided by square of height (27); HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure. * $p < 0.05$, compared with baseline.

large artery distensibility in patients with essential hypertension, and to research the possible therapeutic use of long-acting nitrates in combination with other anti-hypertensive medications. PWV, which has been confirmed as a reliable index of arterial distensibility, was here chosen as a marker for this parameter (8, 9).

Methods

Selection of Patients

From April 1999 to June 1999, 17 patients with essential hypertension (10 men and 7 women; mean age, 62.53 ± 7.94 years, range, 47 to 78 years) attending the outpatient clinic of Ruijin hospital (Shanghai) were asked to participate in this study. Exclusion criteria were the presence of renal or hepatic disease, chronic heart failure, positive history or clinical signs of ischemic heart disease or diabetes mellitus. Diagnosis of essential hypertension was made by the attending physician after complete medical history, physical examination and routine biochemical analysis of blood and urine were obtained from each patient. Further investigation was carried out only when abnormalities were found in these analyses or when other symptoms or signs suggesting secondary hypertension were present. All selected patients had grade 1 to grade 2 essential hypertension with a blood pressure (BP) of 140–179 mmHg systolic BP and/or 90–109 mmHg diastolic BP were included (10). All patients were undergoing anti-hypertensive therapy, six of them had received angiotensin converting enzyme inhibitor for 1 to 2 years, 1 had received β -blocker for 1 years, and 10 had received calcium channel blocker for 1 to 3 years.

Design

The pilot study was of longitudinal design, consisting of two 2-week intervals. All patients continued their anti-hypertensive medication together with IS-5-MN administration at the time of the study. Before IS-5-MN treatment, PWV, blood pressure, height, body weight, and

heart rate were recorded. Oral administration of IS-5-MN (one 30 mg tablet at 8 AM; Astra, Wuxi, P.R.China) was then started, and follow-up examinations were given at 2 and 4 weeks at 2 h after IS-5-MN administration. At every visit, after 15 min rest, blood pressure was measured in the seated position, using the right arm. The clinic BP was defined as the average of three readings separated by 2 min. Phases I and V of the Korotkoff sounds were taken as the SBP and DBP, respectively. During treatment, 6 patients complained of headache, but no drug restriction was necessary, since this symptom disappeared 2 to 6 days later. All selected patients gave their informed, written consent prior to participation in the study.

Pulse Wave Velocity Measurement

Assessment of arterial distensibility was made using an automatic PWV system (Complior, Colson, France). Auto PWV measurement is a standardized, repeatable method (8, 9). It is based on a simple technique, which consists of recording pressure wave forms at two different arterial sites. The pulse transit time between the two recording sites is related to the distance between the two points of measurement. Knowing the distance and pulse transit time, the velocity can be calculated. PWV can be measured between any two points of the arterial tree. In this trial the carotid-femoral PWV was chosen. The PWV was measured automatically, as described in detail by Asmar *et al.* (8), using a pressure transducer with a large-frequency bandwidth. The on-line computerized measurements were analyzed using an algorithm based on the time-shifted and repeated linear correlation calculation between the initial rise in the pressure wave forms. Patients were placed in the recumbent position, and, after 10 min rest, left carotid-femoral PWV was measured. Sixteen measurements were used for the calculation of the mean velocity.

Statistical Analysis

Data are presented as the means ± SD. One-way analysis

of variance (ANOVA) was used to analyze data from patients among the three groups and the effect of IS-5-MN therapy at 2 weeks and 4 weeks followed by Bonferroni multiple comparison test. Value of $p < 0.05$ were considered to indicate statistical difference.

Results

No significant differences were observed in the levels of body mass index, systolic, diastolic, mean or pulse blood pressure or heart rate among the baseline, 2 weeks and 4 weeks examination (Table 1). Carotid-femoral PWV were lower at the 2 weeks and 4 weeks examination than at baseline ($p < 0.05$, $p < 0.05$, respectively). At 4 weeks, however, carotid-femoral PWV was higher than that at 2 weeks, but the difference was not statistically significant (Table 1).

Discussion

Large arterial stiffness is the major determinant of left ventricular afterload, central aortic peak systolic pressure, and prognostic cardiovascular complications. Sustained increase in blood pressure often leads to stiffness of the large arteries. The increased stiffness aggravates hypertension by increasing systolic blood pressure and can induce cardiac hypertrophy and arterial lesions (5). Stiffening of large arteries is associated with excess morbidity and mortality independently of other cardiovascular risk factors (5). Distensibility and compliance are the two most widely used markers of arterial stiffness. Automatic PWV measurement has been demonstrated a good parameter to reflect arterial distensibility (8, 9). In our pilot study, PWV was chosen as an index to reflect large artery distensibility. Arterial compliance decreases with increased blood pressure or increased wall stiffness (5). Each class of antihypertensive drug has different modes of action (6). Studies have demonstrated that angiotensin-converting enzyme inhibitors, calcium antagonists, and nitrates can all improve arterial distensibility (11-13).

The aim of the present study was to assess the effect of IS-5-MN for 4 weeks administration on the changes in PWV after a single dose of 30 mg. In order to observe the additional effect of IS-5-MN, all patients maintained their previous antihypertensive treatment during the study period. The trial was performed in patients with grade 1 to grade 2 essential hypertension. The carotid-femoral PWV was used for the determination of arterial distensibility.

The main results were as follows: 1) the PWV decreased significantly after a single oral dose of IS-5-MN. 2) IS-5-MN did not have a significant effect on the change in brachial pressure. 3) IS-5-MN had a long effective role, had no significant side effects and showed obvious drug resistance.

Nitroglycerin and the long-acting nitrates have been used in cardiovascular medicine for over 100 years. Ni-

trates are widely utilized for the various anginal syndromes and are also used in congestive heart failure and patients with left ventricular dysfunction. At present, nitrates remain the initial treatment for relief or prevention of angina in patients with coronary artery disease. The potential mechanisms of nitrates artery function include the formation of nitric oxide (NO) within vascular smooth cells. NO stimulates the enzyme guanylate cyclase, which results in increases in cyclic guanosine monophosphate and vasodilation (14-16).

Nitrates have been shown to improve artery compliance in patients with essential hypertension due to their reduction of wave reflection independent of brachial blood pressure. Thus systolic pressure in the central arteries can be reduced not only by a reduction in arterial stiffness, but also by a reduction inappropriately early wave reflection (17). These beneficial actions on central systolic pressure are not always apparent when pressure is measured in the brachial and other peripheral arteries (17). The present trial confirmed this theory. This is because the reflected wave constitutes the peak of downstroke of the wave in peripheral arteries. Hence sphygmomanometric recordings underestimate the reduction in central systolic pressure and in left ventricular load brought about by nitrate (17).

Nitrate reduced wave reflection was first noted by Murrel in 1879 (18), but the beneficial effects of nitrates on left ventricular load have been systematically underestimated over the years due to the complete reliance placed on cuff sphygmomanometric systolic values (19-21).

We studied the effect of oral administration of long acting IS-5-MN (30 mg), which, unlike the dinitrate, does not require hepatic biotransformation to a vasoactive metabolite. IS-5-MN can maintain effective blood concentration over 24 h, and thus only need to be administered once daily (22). It thus has good potential for treatment of hypertensive patients. In our pilot study, PWV was significantly reduced at 2 weeks and 4 weeks at IS-5-MN treatment. This demonstrated that once-daily administration with nitrates was effective, could be used together with antihypertensive medication in patients with essential hypertension.

In normal subjects and hypertensives, isosorbide dinitrate caused an increase in aortic diameter together with an increase in arterial distensibility; the changes in mean arterial pressure were significant only in hypertensives, indicating that the altered vasodilator response in essential hypertension is not endothelium-mediated. Relaxation produced by nitrates on venous, arteriolar, and large arterial vessels is well known (23).

Laurent *et al.* (24) demonstrated during isosorbide dinitrate administration that common carotid artery compliance increased due to an increase in internal diameter and the augmentation index of the common carotid artery distension waveform was significantly reduced, suggesting

a reduction in wave reflection by nitrates. In our study, the reduction in PWV was significant after 2 weeks and 4 weeks IS-5-MN oral administration, while there was no change in brachial blood pressure. Reduced wave reflection could partly explain the results.

Conclusions

Nitrates derivatives are useful drugs because of their direct vasodilating properties. This is particularly valuable in the great arteries, explaining the improvement in arterial compliance regularly observed. The corollary of this effect is an improvement in large arterial distensibility with little change in peripheral arterial pressure. This improvement reduced myocardial systolic stress and ensures relative preservation of coronary perfusion pressure, which is particularly important in the treatment of systolic hypertension of the elderly (25, 26). Long acting nitrates are effective drugs in reducing wave reflection and relaxing vessel smooth muscle cell, thereby reducing large arterial rigidity and increasing large arterial distensibility. These drugs could be used in combination with other antihypertensive drugs in the future in the antihypertensive field.

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