Effects of Isosorbide Mononitrate and AII Inhibition on Pulse Wave Reflection in Hypertension

Gordon S. Stokes, Edward S. Barin, Kerry L. Gilfillan

Abstract—The aortic pulse wave contour in isolated systolic hypertension often shows a prominent reflection peak, which combines with the incident wave arising from cardiac ejection so as to widen pulse pressure. We investigated the effects of an extended-release nitrate preparation and of 2 angiotensin II (AII) inhibitors (an AII receptor antagonist and an ACE inhibitor) on the aortic pulse wave contour and systemic blood pressure in hypertensive subjects with high augmentation index caused by exaggerated pulse wave reflection. Two double-blind, randomized, placebo-controlled crossover studies were carried out in a total of 16 elderly patients with systolic hypertension resistant to conventional antihypertensive therapy. In 1 study, pharmacodynamic responses to single doses of placebo, isosorbide mononitrate, eprosartan, and captopril were determined; in the other, single-dose isosorbide mononitrate and placebo were compared in subjects treated with AII inhibitors at baseline. Blood pressure was measured by applanation tonometry and pulse wave components by applanation tonometry at the radial artery. All 3 agents were shown to decrease brachial systolic blood pressure, aortic systolic blood pressure, and aortic pulse pressure. Qualitative effects on the aortic pulse wave contour differed: augmentation index was not significantly altered by either captopril or eprosartan but was decreased (P<0.0001) by ≈50% of the placebo value with isosorbide mononitrate in both study groups. We propose that isosorbide mononitrate corrected the magnified wave reflection in systolic hypertension of these elderly patients by an effect that was distinct from that exercised by either acute or chronic AII inhibition. (Hypertension. 2003;41:297-301.)

Key Words: angiotensin antagonist ■ antihypertensive therapy ■ elderly ■ hypertension, arterial ■ isosorbide mononitrate ■ pulse wave

Isolated systolic hypertension (ISH) and associated widening of pulse pressure have been identified as important risk factors for cardiovascular disease in the elderly and may persist despite the use of conventional antihypertensive drugs. A hierarchy of clinical responses to such therapy has been reported: Calcium antagonists produced the most significant antihypertensive effect, followed by diuretics, ACE inhibitors, and β-blockers. A place for nitrates in this hierarchy has been surmised for more than a decade but has not been clearly established. The high pulse pressure of ISH is usually associated with the presence in the aortic pulse wave of a prominent reflection peak, long known to be nitrate-sensitive, which combines with the tail of the incident peak arising from cardiac ejection to increase pulse pressure. We showed in a previous study that the amplitude of this wave reflection, measured by applanation tonometry, could be decreased by the use of isosorbide mononitrate (ISMN) given as an adjunct to conventional combined antihypertensive therapy. This effect was associated with sustained lowering of systolic blood pressure during continued once-daily administration of extended-release ISMN. However, selection bias may have influenced our findings because the patients had been demonstrated to respond to nitrates before study entry; also, the efficacy of other antihypertensive agents relative to that of ISMN was not tested.

In this study, we compared the antihypertensive activity and effects on pulse wave contour of single doses of ISMN, captopril, and eprosartan in a group of nitrate-naive elderly patients with systolic hypertension. In a similar group, responses to ISMN were studied also in the presence of chronic treatment with angiotensin II inhibitors.

Methods

The subjects were 16 patients with long-standing hypertension, referred from their family physicians after having undergone treatment trials with a variety of conventional antihypertensive agents without reaching satisfactory control of systolic blood pressure. One subject had a history of unilateral renal artery stenosis successfully treated by angioplasty; in the remainder, causes of secondary hypertension had been excluded by routine screening tests. Plasma creatinine concentration was <0.15 mmol/L in every case. There was a history of myocardial infarction or coronary bypass grafting in 4 subjects, of peripheral vascular disease in 4, and of diabetes mellitus (not requiring medication) in 1. Six subjects were receiving treatment for hypercholesterolemia with lipid-lowering drugs (HMG-CoA reductase inhibitors) and had a mean serum total cholesterol concentration of 4.9 mmol/L (range, 3.8 to 6.5). The remainder
Two different study protocols were used. One patient participated in both protocols, with a 15-month break between. Entry to either study required that systolic blood pressure should be between 150 and 200 mm Hg and that diastolic blood pressure should be ≤100 mm Hg. The diastolic cutoff value, which exceeded that of 90 mm Hg in the 1999 World Health Organization guidelines for defining ISH,14 was chosen to allow for minor downward fluctuation in blood pressure between the time of study randomization and the first study day.

**Group 1 Protocol**

A double-blind, randomized, crossover study of the 3 study drugs and a placebo was carried out in 11 of the subjects, 5 men and 6 women, 59 to 82 years of age (mean, 69.8). Their baseline antihypertensive therapy had been stable for 3 weeks or more and was continued unchanged as baseline treatment through the present study. None had received nitrates therapy previously.

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**Group 2 Protocol**

Six patients, 3 men and 3 women, 59 to 81 years of age (mean, 72.8) (one of whom also participated in group 1), had a randomized, double-blind crossover study in which 60 mg ISMN was given at 8:00 AM on 1 day and placebo was given at 8:00 AM on the other. The 2 study days were 1 to 2 weeks apart. Observations were made from 8:00 AM to 4:00 PM as in group 1. These subjects differed from group 1 in that they were receiving treatment at study entry with ACE inhibitors or AII receptor antagonist drugs, as follows: 10 mg/d fosinopril (1 case), 50 mg/d captopril (1), 10 mg/d ramipril (1), 10 mg/d ramipril and 16 mg/d candesartan (1), 300 mg/d irbesartan (1), and 40 mg/d telmisartan (1). Their other baseline antihypertensive drug therapy consisted of 1 to 2 of the following agents in conventional dosages: hydrochlorothiazide (1), β-blockers (2), amlo- dipine (1), and diltiazem controlled-delivery formulations (2). Three were receiving HMG CoA reductase inhibitors (including the patient who participated earlier in group 1).

The study was approved by the institutional ethics committee. Written informed consent was obtained from all subjects. Brachial blood pressure was recorded by sphygmomanometer, and pulse wave tonometry was performed at the radial artery with the patient seated. The aortic pulse waveform was derived mathematically from the measurements made at the radial artery site. From the waveform, the aortic first peak pressure (P1) and augmentation pressure (P2) were quantified by computer software (SphygmoCor, AtCor Medical), as previously reported.12 Augmentation index (P2 expressed as percentage of pulse pressure) described the magnitude of wave reflection. Statistical analysis was by repeated-measures ANOVA, with the use of PRISM (GraphPad Software Inc) and post hoc paired t tests. Drug carry-over effect was assessed with treatment order used as the independent variable. Values given are mean±SEM.

**Results**

The effects in group 1 of single doses of ISMN, captopril, and eprosartan on aortic systolic blood pressure and augmentation index are shown in Figure 1, and those on brachial blood pressure and heart rate are shown in the Table. There was no significant treatment-order effect. All 3 agents significantly decreased aortic systolic blood pressure (for ISMN and captopril, P<0.0001; for eprosartan, P<0.0001), and this effect was greater with ISMN than with captopril or eprosartan (P<0.0001). At the respective nadirs of hypotensive effect for the 3 agents, the aortic systolic pressure was lower than control by 34 mm Hg (P<0.001) with ISMN (10:00 AM), by 23 mm Hg (P<0.001) with captopril (11:00 AM), and by 15 mm Hg (P<0.05) with eprosartan (9:00 AM). Corresponding decrements in aortic pulse pressure were 29 mm Hg (P<0.001), 18 mm Hg (P<0.001), and 10 mm Hg (P<0.05), respectively.

Separation of the effect on aortic pulse pressure into P1 and P2 components showed that eprosartan, captopril, and ISMN
each produced small decreases in P1 (at nadir, 4±2, 9±2 and 10±2 mm Hg, respectively) that were not significantly different between agents. However, the decrease in P2 was significantly greater (P<0.0001) for ISMN (at nadir, 19±3 mm Hg) than for captopril (9±3 mm Hg) or eprosartan (6±3 mm Hg). Augmentation index was significantly decreased by ISMN (P<0.0001) throughout the postdose observation period, but the minor decrements observed with captopril and eprosartan were not significant (Figure 1).

All 3 agents significantly decreased sitting and standing brachial systolic blood pressure (P<0.005) with little extra orthostatic effect (Table). For ISMN, the falls in brachial systolic pressure values were much greater than those in brachial diastolic pressure and were more prolonged than the corresponding effects observed with the other 2 agents; time trends were similar to those for aortic systolic blood pressure (Figure 1). Heart rate was not changed by captopril or eprosartan but showed a minor increase late in the observation period with ISMN. Baseline (8:00 AM) heart rate on the ISMN study day was 62±4 bpm, remained steady between 60 and 62 bpm from 10:00 AM to 1:00 PM, and increased to values of 65±5 bpm at 3:00 and 4:00 PM.

Figure 2 shows the effects of single doses of ISMN on aortic systolic blood pressure and augmentation index for group 2 (6 patients with baseline therapy that included AII inhibition). The mean control values (placebo day, 8:00 AM to 4:00 PM) for aortic systolic blood pressure and augmentation index were 154±2 mm Hg and 38.5±1.1%, respectively. For comparison, the corresponding values for group 1 were 160±2 mm Hg and 37.9±1.0%. Both aortic systolic pressure and augmentation index decreased significantly with ISMN in group 2 (P<0.0001); the average postdose decreases were, respectively, 34±3 mm Hg and 16±1%, in comparison to decreases of 29±2 mm Hg and 15±1% in group 1. Sitting and standing brachial systolic blood pressure in group 2 were each decreased by ISMN (P<0.0001). Sitting brachial systolic blood pressure decreased from control values of 176 mm Hg at noon and 173 mm Hg at 4:00 PM, by 37 and 34 mm Hg (P<0.001), respectively. Corresponding decreases for sitting diastolic pressure (13 and 10 mm Hg) and for standing systolic and diastolic blood pressure were not significant at these time points. Heart rate was increased overall from a mean value of 60 to 64 bpm (P<0.001). However, this was due in part to a slightly higher baseline value on the ISMN study day (66±4) than on the placebo day (63±3).

Discussion

Our studies were carried out in a high-risk population. Treatment trials in the elderly have shown that uncontrolled systolic hypertension has a high morbidity rate from strokes and coronary vascular disease.1–3 The ethical criterion justi-
fying entry of patients to the present study was that they had been treated by their personal physicians with a range of conventional antihypertensive agents (singely and in combination) and either had not tolerated the therapy or had failed to show an adequate response in systolic blood pressure. Their treatment regimens at study entry had proved the most effective available for them to date and were left unchanged for at least 3 weeks before entry to ensure a steady albeit still elevated baseline of systolic blood pressure. The use of a placebo on 1 study day and the use of an unorthodox blood pressure–lowering drug (the nitrate) on another imposed no additional hypertensive risk, for their preceding regimens were not withdrawn. Conversely, to have regularized baseline therapy so that each patient’s prestudy regimen was the same or to have prolonged investigation by performing multidose studies was believed to be impracticable and potentially unethical. However, with the use of single-dose studies, it proved feasible (a) to confirm that the effects of ISMN on pulse wave reflection contributed to lowering pulse pressure and systolic pressure, and (b) to determine whether these effects were matched by or were additive to those of AII inhibitor agents.

ISMN was shown to reduce systolic blood pressure strongly in this series of nitrate-naive patients, with minor effects on diastolic blood pressure and heart rate. The findings were similar to those obtained after ISMN therapy for 2 weeks or periods of up to 5 years of continuous ISMN therapy in subjects with previous nitrate exposure. Studies with nitroglycerin infusion have shown an accentuated hypotensive response during standing; in our study, there was a mild orthostatic effect with ISMN, which was not greater than with the other 2 agents given.

The nadir hypotensive effect of each agent (in relation to placebo) occurred 1 to 3 hours after dosing (Figures 1 and 2). This was within the time to reach peak plasma concentration reported for ISMN (3 to 4 hours) and eprosartan (1 to 2 hours) but slightly later than that reported for captopril (1 hour). The effect of ISMN (which was in an extended-release preparation) was well sustained through the remainder of the observation period; that of the other agents diminished, consistent with their shorter elimination half-lives.

The decreases in aortic systolic pressure and aortic pulse pressure with ISMN were due partly to a reduction in amplitude of the prominent pulse wave reflection found in these patients, as indicated by a decrease in augmentation index at nadir of ~50% of control (Figures 1 and 2). These findings were not attributable to the minor cardioacceleration produced by ISMN late in the observation period, for heart rate with ISMN at the nadir was unchanged from that with placebo (Table). In these parallel studies of the short-term effects of ISMN, captopril, and eprosartan on aortic pulse wave contour, ISMN was observed to have a nadir effect on the P1 (first peak) component of pulse pressure that was not significantly different from that of the AII inhibitors. However, the nitrate had a greater effect on P2 (augmentation) pressure. Integration of these data as augmentation index (Figure 1, right) rendered the marked difference in the effects of the drugs on wave reflection more evident.

This study examined the short-term effects of single doses. With the doses that we selected, the fall in systolic blood pressure was greater for ISMN than for captopril or eprosartan. The question that arises is whether steady-state conditions and the use of higher doses of AII inhibitors in group 1 could have resulted in decreases in systolic blood pressure and augmentation index to the levels observed with ISMN.

A review of reported studies indicated that acute or chronic treatment with moderate or high dosages of AII inhibitors has been generally associated with decreases in augmentation index of lesser magnitude than the decrement of 20% observed with ISMN in the present study. The effects of captopril at steady state were reported by Mahmud and Feely, who showed in hypertensive patients (average age, 49 years) treated for 4-week periods that augmentation index was decreased by 4% with 50 mg daily and by 9% with 100 mg daily. In another steady-state study, 10 to 20 mg fosinopril daily lowered the index in hypertensive patients (mean age, 46 years) by 9%. In a study of design similar to our study and with patients of the same age, a single 10-mg dose of ramipril decreased the index by 7%. In a group of hypertensive men (mean age, 27 years), 600 mg eprosartan daily for 1 week decreased the augmentation index by 7%. Valsartan (80 mg daily and 160 mg daily) decreased the index at steady state in hypertensive patients (mean age, 49 years) by 4% and 5%, respectively. Telmisartan (40 mg daily) decreased the index at steady state by 2.3% in an elderly hypertensive group. These reported findings, together with those from the present study, indicate that AII inhibitors may not be as effective as ISMN in decreasing wave reflection. It has been suggested that augmentation index may reveal the extent of endothelial dysfunction in vivo. Such dysfunction is thought to occur in essential hypertension and was suspected in the present patient series because of high augmentation index at baseline, a history of long-standing hypertension, hypercholesterolemia in 12 of the 16 cases, and a background of known vasculopathy in 8. AII inhibitor therapy has been reported to improve endothelial dysfunction and decrease wave reflection. However, ISMN appeared to correct the process giving rise to magnified wave reflection in this series of patients by an effect distinct from that exercised by either acute or chronic AII inhibition. Thus, there was no overlap evident between the effect on wave reflection of chronic AII inhibition and that of ISMN: the fall in augmentation index resulting from ISMN in group 2 (who were treated at baseline with AII inhibitors) was comparable with that in group 1 (who were not). Other differences in baseline therapy between groups, which could have had a role in this outcome, were not substantial. Calcium channel blockers, reported to improve endothelium-dependent vasodilation, were used in the baseline regimen in 9 of 16 patients studied. HMG CoA reductase inhibitors, also reported to improve endothelial function, were used in 6. However, the proportion of patients in group 1 receiving these 2 drug classes (55% and 36%, respectively) was comparable to that in group 2 (50% for both).

ISMN is a prodrug that undergoes enzymatic degradation in the vascular smooth muscle cell to form nitric oxide (NO), which acts through cGMP-mediated processes to produce endo-
helium-independent vasodilation in muscular arteries. The level of the arterial tree at which the effect of NO donors on wave reflection is operative has been a subject of some controversy. In the normal circulation, vasorelaxation after nitrate administration is greater in conduit arteries than in major central arteries or in arterioles.9 Moderate changes in brachial artery compliance and total peripheral resistance have been shown in healthy volunteers with the NO donors isosorbide dinitrate and nitroprusside.32 However, in hypertensive cardiovascular disease, the muscle layer of larger arteries is progressively replaced by collagen, whereas the muscular layer of small arteries becomes hypertrophied. These developments may tend to shift the foci of reflection distally to the smaller conduit arteries and arterioles, where nitrate-induced dilation could produce relatively larger changes in the peripheral vascular resistance and in the amplitude of wave reflection.

Perspectives
It has been suggested that shear stress generated by each pulse wave excites release of a spurt of endothelial NO, causing vasodilation in muscular arteries.33,34 We postulate that this allows forward progression of the pulse volume more distally into vascular beds and limits the amplitude of wave reflection. With endothelial dysfunction, pulsatile NO production is impaired. The pulse wave impacts a tonically constricted small artery network; the resulting recoil induces an amplified wave reflection, which is a major contributor to the expanded pulse pressure of ISH. NO donors such as ISMN diminish the recoil and modulate wave reflection. However, with antihypertensive drugs requiring intact endothelial NO production for their actions to be mediated, a beneficial effect on wave reflection may be delayed until endothelial recovery has occurred.

References
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