Long-Term Effectiveness of Extended-Release Nitrate for the Treatment of Systolic Hypertension

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***Abstract*—**Isosorbide mononitrate (ISMN) is effective in the short-term for decreasing systolic blood pressure, pulse pressure, and pulse wave reflection in patients with systolic hypertension. To determine whether tolerance negates the efficacy of this nitrate in the long-term, a placebo-controlled study was performed in which ISMN was withdrawn briefly in a group of patients (n=16) who had received extended-release ISMN 60 to 120 mg once daily for 16 to 109 months. Blood pressure and wave reflection were determined by 24-hour ambulatory recorder and tonometer, respectively. During a 4-hour delay of the regular morning dose of ISMN, mean systolic blood pressure was higher than with the regular ISMN dosing schedule ($P<0.0001$). The maximum placebo-active difference was 16±4 mm Hg. The corresponding difference in augmentation index (a measure of pulse wave reflection) corrected for heart rate was 25±4% ($P<0.001$). The difference in pulse pressure was 13±3 mm Hg ($P<0.001$). There was no significant difference in diastolic blood pressure. For a subgroup (n=12) in which the effects of a single ISMN dose had been determined at the initiation of regular ISMN therapy, the mean change in augmentation index was of similar magnitude to that observed in their initial study. Thus, tolerance does not seriously diminish the antihypertensive efficacy of ISMN used as adjunct therapy in the chronic treatment of systolic hypertension. This agent lowers systolic blood pressure sufficiently to achieve therapeutic goal in some patients refractory to conventional treatment regimens. **(*Hypertension*. 2005;45:380-384.)**

Key Words: antihypertensive therapy ■ hypertension ■ arterial pressure ■ nitric oxide

Uncontrolled systolic hypertension is an important risk factor for stroke and heart attack in the elderly and is often refractory to treatment with established antihypertensive agents.[1] Characteristic of this condition is a high arterial pulse pressure that results from effects of aging and age-associated cardiovascular disease on the arterial wall.[2] With advancing age, there is large artery stiffening that reduces arterial compliance and increases the velocity of transmission of the reflected component of the pulse wave so that it moves in timing from diastole to late systole.[3] Additionally, there is small artery constriction that increases the magnitude of reflection.[3] The reflection combines with the ejection component of the pulse wave, thereby boosting pulse pressure and systolic pressure.

The changes in arterial wall function may derive from endothelial dysfunction,[4] including deficiency in endogenous nitric oxide generation.[5,6] Exogenous nitrate has been shown to reverse these changes, resulting in increased arterial compliance, vasodilatation, and decreased systolic blood pressure.[7] An attractive concept, articulated more than a decade ago[8] and still topical,[9] is that nitric oxide donors could be administered therapeutically in hypertensive patients to obtain a predominant decrease in systolic blood pressure. Such an effect has been reported from short-term trials in elderly patients with isolated systolic hypertension using extended-release formulations of either isosorbide dinitrate or isosorbide mononitrate (ISMN).[10–15] However, evidence for long-term antihypertensive efficacy with ISMN is rather limited,[1,15] and there have been no controlled trials to determine whether ISMN exercises a preventative effect on morbid cardiovascular events in hypertension.

It has been argued that tolerance to the actions of nitrates like ISMN may appear if they are used long-term to treat arterial insufficiency states such as angina pectoris.[16] However, tolerance was not detected with isosorbide dinitrate when used to treat systolic hypertension in the elderly.[17] For 9 years, we have used ISMN as an adjunct in treating selected patients with refractory systolic hypertension. We recalled a group of these patients and determined in a randomized crossover study against placebo whether ISMN exhibited long-term antihypertensive efficacy. Also, we determined whether the effects on arterial pulse wave reflection and arterial stiffness, which are characteristic of ISMN, persisted with long-term ISMN treatment.

Subjects and Methods

The subjects were 16 elderly patients with long-standing hypertension. All were fully ambulant without symptomatic cardiac disease or known vascular aneurysm. One subject had a history of unilateral renal artery stenosis successfully treated by angioplasty and 1 had mild primary aldosteronism without adrenal lateralization; in the remainder, causes of secondary hypertension had been excluded by

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TABLE 1. Patient Characteristics

Clinical Data	No.	%
Total	16	100
Age (mean [range]), y	72 [64–83]	
Men	7	44
Previous ischemic heart disease	4	25
Previous stroke	2	12.5
Treatment with HMG CoA reductase inhibitors	8	50
Pre-ISMN antihypertensive therapy*		
Combination of 2 agents	6	37.5
Combination of 3 agents	6	37.5
Combination of 4 agents	4	25
Dose of ISMN (as adjunct)		
60 mg per day	7	44
120 mg per day	9	56

*Two to 4 agents, each from a different class: diuretic (n=14), β blocker (n=7), calcium channel blocker (n=12), angiotensin-converting enzyme inhibitor (n=4), angiotensin II receptor blocker (n=8), sympatholytic (n=1).

routine screening tests. Plasma creatinine concentration was <0.15 mmol/L in every case. Further characteristics are shown in Table 1. Eight patients receiving treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for hyperlipidemia had a mean total serum cholesterol concentration of 4.7 mmol/L (range, 4.3 to 6.5). The remainder (n=8) had a mean total serum cholesterol concentration of 5.0 mmol/L (range, 3.5 to 6.3). All the subjects were referred from their family physicians after having undergone treatment with various regimens of conventional antihypertensive agents given singly and in combination; none of these regimens had controlled systolic blood pressure adequately. ISMN had been shown to provide an additional antihypertensive effect when added to the most effective of the antihypertensive regimens that was tolerated by the patient. The antihypertensive therapy immediately before starting ISMN (Table 1) consisted of 2 to 4 of the following drugs, administered in conventional dosage: diuretics (hydrochlorothiazide 25 to 12.5 mg/d [8 cases], amiloride 5 mg/d [2 cases], indapamide 2.5 mg/d [3 cases], aldactone 50 mg/d [1 case]); β-blockers (atenolol 50 to 100 mg/d [4 cases], metoprolol 50 mg/d [1 case], sotalol 160 mg/d [1 case], pindolol 10 mg/d [1 case]); calcium channel blockers (amlodipine 5 to 7.5 mg/d [2 cases], lercanidipine 5 to 10 mg/d [2 cases], controlled-release formulations of diltiazem 240 mg/d [2 cases] or nifedipine 30 to 120 mg/d [6 cases]); angiotensin-converting enzyme inhibitors (ramipril 10 mg/d [1 case], perindopril 4 mg/d [2 cases], monopril 10 mg/d [1 care]); angiotensin II receptor antagonists (candesartan 4 to 32 mg/d [4 cases], irbesartan 300 mg/d [3 cases], telmisartan 40 mg/d [1 case]); and sympatholytic (prazosin 2 mg/d [1 case]). Additionally, all patients had received extended-release isosorbide mononitrate, 60 to 120 mg in the morning, for a continuous period of 16 to 109 months (mean, 48 months) up to the time of the present study.

At least 1 week (usually 1 month) before the time of entry to the present study, the dosing schedule of the antihypertensive therapy for each patient had been rearranged so that medication other than ISMN was taken in the late afternoon or evening. This regimen was continued unchanged as baseline treatment through the present study.

Protocol

A double-blind randomized crossover study of ISMN and a placebo was performed in each subject. The dose of ISMN was either 60 mg or 120 mg ISMN (determined by the dosage used in preceding long-term therapy). Encapsulated single doses of ISMN (extended-release preparation; AstraZeneca, Australia) were given on 2 study days, each separated from the next by 1 to 2 weeks. On one study day, the active ISMN dose was given at 8:05 AM, followed by a placebo at 12:05 PM (sequence A); on the other study day, the placebo was given at 8:05 AM and the active ISMN was given at 12:05 PM (sequence B). The rationale was that a 4-hour delay in the usual time of dosing would be sufficient to reveal the presence of ongoing effectiveness of the nitrate without exposing high-risk patients to undue increases in systolic blood pressure. Ambulatory blood pressure recording for a 24-hour period was commenced at 4:00 PM on the day before each study day to determine by comparison between days the effect of the dosing delay (Figure 1). Between observations on study days, the subjects engaged in sedentary recreational activities in a temperature-controlled environment. A light meal was given at 12:30 PM.

The study was approved by the institutional ethics committee. Written informed consent was obtained from all subjects. Ambulatory blood pressure was measured by an automated monitor (Meditech, Budapest, Hungary). The monitor was set to record at 30-minute intervals from 4:00 PM to 10:00 PM and from 6:00 AM to 8:00 AM the next day, at hourly intervals overnight between 10:00 PM and 6:00 AM, and at 15-minute intervals from 8:00 AM to 4:00 PM. The average blood pressure for each hourly period was determined for use in data presentation and analysis. Brachial blood pressure (average of 3 readings) was also recorded by a sphygmomanometer to allow calibration of pulse wave tonometry; this was performed on the radial artery at 8:00 AM, 12:00 PM, and 4:00 PM, with the patient seated. The aortic first peak pressure (P1) and reflection peak (P2) were determined from the aortic pulse waveform by computer software (SphygmoCor; AtCor Medical, Sydney, Australia), as previously reported.[12] Augmentation index ([P2÷P1] %) described the magnitude of wave reflection; values cited from published work were transformed from an alternative expression of the augmentation index ([P2−P1]÷pulse pressure %). Statistical analysis was by repeated measures analysis of variance using PRISM (GraphPad Software Inc, San Diego, Calif) and post-hoc paired *t* tests. Values given are mean±SEM.

Results

Mean 24-hour values for ambulatory systolic blood pressure and diastolic blood pressure were not significantly different between sequence A (136±3 and 67±2 mm Hg, respec-

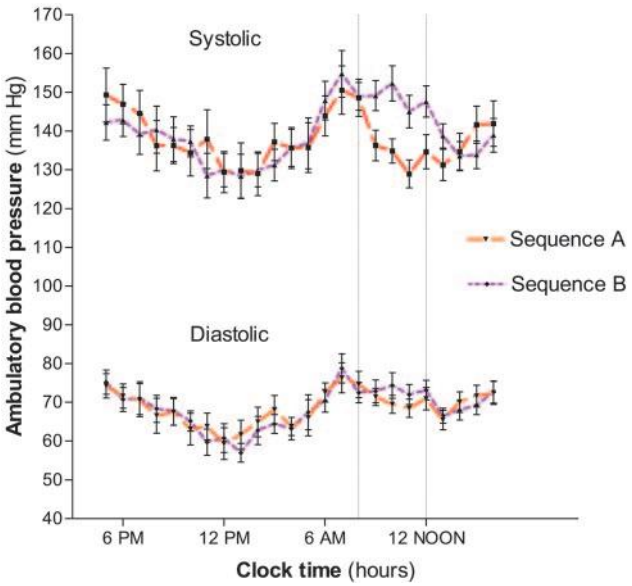

Figure 1. Mean values and SEM (n=16) for 24-hour ambulatory blood pressure (systolic and diastolic) with treatment on different study days with sequence A (active ISMN at 8:05 AM and placebo at 12:05 PM) and sequence B (placebo at 8:05 AM and active ISMN at 12:05 PM). Dotted lines show times of ISMN/placebo administration.

TABLE 2. Mean Values±SEM for Ambulatory Blood Pressure and Heart Rate for the Period 8:00 AM to 12:00 PM After a Dose of ISMN (Schedule A) or Placebo (Schedule B) at 8:00 AM in 16 Patients

		Time of Day				
	Variable	8:00 AM	9:00 AM	10:00 AM	11:00 AM	12:00 PM
Systolic blood pressure, mm Hg	A	149±5	137±4	135±3	129±4	135±4
	B	149±4	149±4*	152±5*	145±4*	148±4*
Diastolic blood pressure, mm Hg	A	75±3	71±2	70±2	69±2	71±3
	B	73±3	73±3	74±3	72±3	73±3
Arterial pulse pressure, mm Hg	A	74±4	67±3	65±3	60±3	64±4
	B	76±3	75±3*	78±4*	73±3*	75±4*
Heart rate, bpm	A	66±3	65±3	64±3	65±3	65±3
	B	65±3	62±3	62±3	60±3*	63±3

* $P<0.01$.

tively) and sequence B (140±3 and 65±2 mm Hg); also, there was no order effect. Thus, the switch in active ISMN dosing from 8:05 AM to12:05 PM had no statistically significant effect on the overall 24-hour average level of blood pressure (from 4:00 PM to 4:00 PM). Figure 1 shows that both systolic blood pressure and diastolic blood pressure declined during the night and increased during the period from 5:00 AM to 7:00 AM. There was no appreciable hour-to-hour difference between sequences A and B for diastolic blood pressure throughout the 24-hour monitoring period, or for systolic blood pressure between the start and 8:00 AM. However, in the period from 9:00 AM to 12:00 PM, systolic blood pressure (n=16) was lower ($P<0.0001$) for sequence A than for sequence B. Table 2 shows that at the nadir of sequence A (11:00 AM to 12:00 PM), the difference in mean systolic blood pressure between sequences was 16±4 mm Hg ($P<0.001$). Pulse pressure was also lower for sequence A, with a difference between sequences of 13±3 mm Hg at nadir ($P<0.001$). Mean values for ambulatory diastolic blood pressure were not significantly different between sequences. Mean heart rate at nadir was 5 bpm higher for sequence A ($P<0.01$). During the period from 1:00 PM to 4:00 PM, there were no differences between the sequences in mean values for systolic blood pressure, diastolic blood pressure, or heart rate.

Mean values for augmentation index at 8:00 AM or 4:00 PM (shown in Figure 2) did not differ between sequences. Augmentation index at 12:00 PM was 132±4% for sequence A and 159±5% for sequence B; the difference was 27±4% ($P<0.001$).

Discussion

"True" biochemical tolerance to nitrates, defined as decreased activity of the nitric oxide–cGMP cascade,[18] has long been recognized as a real or potential problem in treating coronary vascular disease. It is unknown whether tolerance can diminish the long-term response to nitrate use for systolic hypertension. The clinical effects of tolerance are subtle and may be influenced by the type of nitrate used, the presence of a nitrate-free period in dosing schedules,[17] and the coadministration of other therapies.[18] For example, ISMN has been reported to cause less tolerance development in vitro than either nitroglycerin or isosorbide dinitrate.[19] Also, extended-release ISMN when used for angina relief was found to cause tolerance if given twice daily, but not if given once daily (as it was in the present study).[20] Tolerance development to nitrates may be minimized when co-therapy includes sulfhydryl agents, hydralazine, angiotensin-converting enzyme inhibitors, or antioxidant vitamins.[18] Four patients in the present study were receiving angiotensin-converting enzyme inhibitors and thereby could have had enhanced lowering of systolic blood pressure (BP) with ISMN. Diuretics (given to 14 patients)[21] and angiotensin II receptor blockers (given to 8 patients) may also have enhanced the effects of ISMN,[22] whereas beta-blockers (given to 7 patients) may have diminished them.[23]

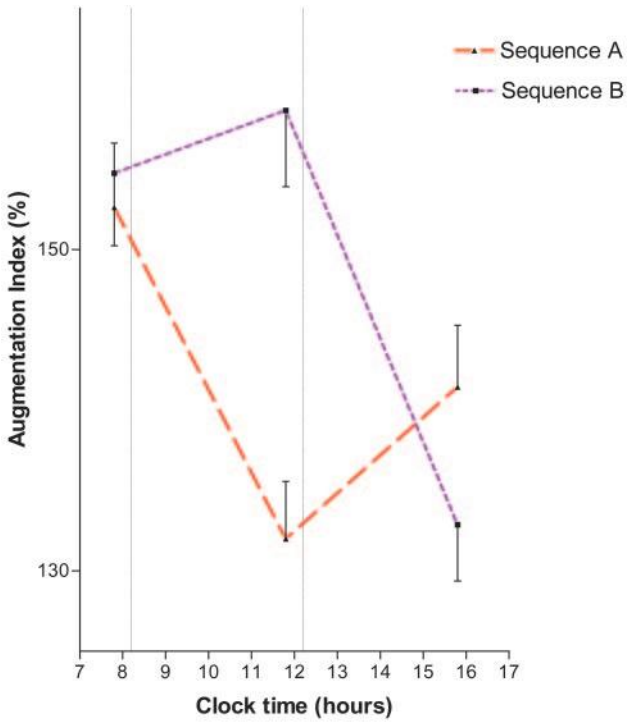

Figure 2. Mean values and SEM (n=16) for augmentation index with treatment on different study days with sequence A (active ISMN at 8:05 AM and placebo at 12:05 PM) and sequence B (placebo at 8:05 AM and active ISMN at 12:05 PM). Dotted lines show times of ISMN/placebo administration.

The present group of subjects was characterized by long-standing systolic hypertension refractory to conventional therapeutic regimens, and by increased aortic pulse wave reflection (before nitrate therapy). On the basis of their marked decreases in systolic BP and augmentation index (a measure of wave reflection) with acute administration of ISMN,[12–15] this agent had been given to them long-term. We have shown previously that during regular once-daily dosing with ISMN 60 to 120 mg, plasma nitrate concentration reached a peak level by 4 hours after dosing and declined to a near-zero concentration by 24 hours.[12] The rationale of the present study was that when a placebo was substituted for the regular nitrate dose, an increase in systolic BP and augmentation index would confirm the existence of long-term response. For ethical reasons, the period of withdrawal of the active agent was restricted to 4 hours.

In this selected group of patients receiving maintenance therapy with a regimen comprising 2 to 4 conventional antihypertensive agents plus extended-release ISMN, the nitrate was found to contribute at nadir a depressor effect of 16 mm Hg in systolic BP and a decrease in pulse pressure of 13 mm Hg. The possibility that these effects were distinctively nitrate-induced[24] was supported by a corresponding pronounced effect on wave reflection, evidenced by a decrease in augmentation index with active ISMN. A correction to the observed decrease in augmentation index is warranted because the accompanying change in heart rate would have influenced the index.[25] For a pacemaker-induced increment of 10 bpm in heart rate, augmentation index declines by ≈4%.[25] Extrapolating this to the present study, in which heart rate at nadir was 5 bpm higher with active ISMN than with placebo, the observed ISMN-induced effect on augmentation index of −27±4% should be corrected to −25±4%.

A limitation of these findings is that demonstration of the continuing effects of ISMN does not exclude the presence of tolerance, because the development of tolerance does not necessarily imply complete abolition of therapeutic effect.[18] In published acute trials, responses to the initial dose of active ISMN (given at 8.00 AM) versus placebo had been determined for 12 of the present subjects.[12–15] Mean values for augmentation index observed in this subgroup at nadir (12:00 PM) were, respectively, 123±3% and 149±4%, with no significant change in heart rate. Thus, the mean ISMN-induced change for augmentation index from the earlier trials was −26±3%. The corresponding effect for the same subgroup in the present study was −28±4%.

The finding that these effects on pulse wave reflection in the subgroup were closely similar to each other and to the response for the whole study group suggests that tolerance to ISMN did not develop during the long-term treatment period. However, this evidence is not conclusive. Wave reflection could have been affected by changes in underlying cardiovascular disease or in co-administered therapy during this period. This possibility is supported by a lack of significant correlation of the initial and long-term responses of augmentation index to ISMN within the subgroup subjects (r^2=0.1313; P>0.2). Thus, our finding that a distinctive response to ISMN persisted with long-term treatment cannot be taken to exclude the possibility of partial tolerance development.

However, the important practical issue clinically is whether long-term ISMN use is effective enough to warrant consideration as an antihypertensive agent in appropriately selected patients. The question arises as to whether the decline in systolic BP attributable to ISMN in this study could justify regular inclusion of the agent in combination therapy of systolic hypertension. The effects of conventional combination therapy on systolic blood pressure in the elderly have been reported from controlled trials.[26–29] Although significant therapeutic responses were shown, the average systolic blood pressure reached with long-term active treatment in these trials exceeded the currently recommended goal of 140 mm Hg. In the Systolic Hypertension in the Elderly Program (SHEP), for example, the average value (±SD) reached at 5 years was 144±19 mm Hg (773 patients).[27] In the Systolic Hypertension in Europe (Syst-Eur) trial, the average systolic blood pressure at 2 years was 151 mm Hg (1285 patients).[29] The percentages of patients failing to reach goal systolic blood pressure was reported as ≈30% in SHEP and 56% in Syst-Eur. It appears from this experience that a strategy that decreased systolic blood pressure by a further 16 mm Hg (equivalent to the nadir effect of extended-release ISMN in the present study) would have been effective in helping to achieve goal in these trials.

Thus, extended-release nitrates have a potential adjuvant role in attempts to improve treatment in refractory cases of isolated systolic hypertension. However, we emphasize that our findings were restricted to patients known to be acute responders to ISMN, who were already receiving a variety of different medications at study entry. Also, the high early morning blood pressure values observed suggest that further work may be required to optimize the distribution of dosing.

Perspectives

We conclude that tolerance did not seriously diminish the efficacy of ISMN when used as adjuvant therapy in the chronic treatment of a group of patients with treatment-refractory systolic hypertension. The long-term antihypertensive efficacy of this agent appears to justify a trial of its use as an adjunct to conventional combined treatment regimens for the prevention of cardiovascular morbid events in patients with isolated systolic hypertension.

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