Clinical Potential of Combined Organic Nitrate and Phosphodiesterase Type 5 Inhibitor in Treatment-Resistant Hypertension

James J. Oliver, James W. Dear, David J. Webb

Abstract—NO donor drugs (eg, isosorbide mononitrate; ISMN) and phosphodiesterase 5 inhibitors (eg, sildenafil) have antihypertensive properties, and the combination can markedly reduce blood pressure (BP). The objective of this “proof-of-concept” study was to investigate the effect on BP of a combination of single oral doses of sildenafil (50 mg) and ISMN (10 mg) in patients with treatment-resistant hypertension. Six subjects with treatment-resistant hypertension were included, and their usual antihypertensive medication was continued during the study. Sildenafil alone, ISMN alone, and the combination all reduced brachial and central aortic BPs compared with placebo. The combination of sildenafil and ISMN produced the largest fall in BP (maximum brachial BP reduction of 26/18 mm Hg compared with placebo), without producing significant adverse effects. ISMN, alone and in combination with sildenafil, also reduced arterial wave reflection and central BP. In summary, in patients with treatment-resistant hypertension maintained on their usual antihypertensive treatment, sildenafil given alone and ISMN given alone both acutely reduced BP. There was additional BP reduction when these drugs were given in combination. In this therapeutically challenging group of patients, the combination of an NO donor drug and a phosphodiesterase 5 inhibitor may represent an effective treatment. Longer studies in larger numbers of patients are now justified. (Hypertension. 2010;56:62-67.)

Key Words: NO ■ cGMP ■ sildenafil ■ isosorbide mononitrate ■ treatment-resistant hypertension

NO causes vasodilation by stimulating vascular smooth muscle soluble guanylate cyclase to convert GTP to cGMP, which, in turn, leads to a reduction in intracellular calcium concentration.1 cGMP is degraded by cGMP-specific, cGMP-binding phosphodiesterase 5 (PDE5), and inhibition of this enzyme enhances vascular smooth muscle relaxation. By stimulating vasodilation within the corpora cavernosa during sexual stimulation, PDE5 inhibitors, such as sildenafil, facilitate penile erection and are useful treatments of male erectile dysfunction.2 Inhibitors of PDE5 are also vasodilators in the systemic circulation. Indeed, we3 and others4 have demonstrated previously that PDE5 inhibitors constitute effective regular antihypertensive therapy in untreated and treated subjects with mild-to-moderate hypertension.

The organic nitrates, such as isosorbide mononitrate (ISMN), are antianginal drugs that dilate arteries and veins through their action as NO donors.5 The simultaneous provision of exogenous NO from organic nitrates and inhibition of cGMP breakdown with PDE5 inhibition can result in substantial blood pressure (BP) reduction, as we have shown previously.6–8 Although these combinations are currently contraindicated, there is the potential that the combination of an NO donor and a PDE5 inhibitor could be exploited clinically to achieve better BP control in patients with treatment-resistant hypertension (TRH).

The aim of the present proof-of-concept study was to investigate the effect on brachial BP of a combination of single doses of sildenafil and ISMN in patients with TRH. In addition, we investigated the effect of the combination on central aortic BP, BP wave reflection, and pulse wave velocity.

Methods
This was a randomized, placebo-controlled, double-blind, 4-way crossover study. It was approved by the local research ethics committee and performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all of the subjects.

Subjects
Potentially suitable subjects with TRH (defined as the failure to achieve goal BP in patients who are adhering to full doses of an appropriate ≥3-drug regimen9) were identified from among the patients attending the Cardiovascular Risk Clinic, Western General Hospital (Edinburgh, United Kingdom). The inclusion criteria were as follows: men or women with a diagnosis of essential hypertension; office blood pressure (BP) >140/85 mm Hg despite treatment with ≥3 antihypertensive drugs10; daytime average ambulatory BP >130/80 mm Hg on the current antihypertensive drug regimen within 6 months of the start of the study; and resistance to treatment proven

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62
by directly observed therapy (described below). Exclusion criteria were as follows: an identifiable underlying cause for hypertension (including Conn or Cushing syndrome, renal artery stenosis, phaeochromocytoma, or coarctation of the aorta); clinically evident coronary artery or cerebrovascular disease; the need to take regular organic nitrates or nicorandil; significant impairment of kidney or liver function; pregnancy; current alcohol or drug abuse; or previous serious drug allergy.

Potentially suitable subjects who agreed to be considered for the study attended a morning screening visit for blood sampling and assessment of the BP response to directly observed therapy, performed to identify patients with poor adherence to their regular antihypertensive medications who could theoretically have experienced perilously large BP reductions with the study drugs. Subjects had not taken their usual morning antihypertensive medications.

After 30 minutes of rest, baseline supine BP was recorded in duplicate. Subjects then took all of their usual medicines under direct observation, and single measures of BP were repeated every 15 minutes for 4 hours. The average systolic and diastolic BPs over the last 2 hours of the observation period were calculated and subjects were excluded from the study if either measurement was >40 mm Hg lower than the average at baseline.

Measurements

Clinic BP and heart rate (HR) were recorded, with an appropriately sized cuff, using a validated oscillometric sphygmomanometer, the Omron HEM-705CP.11 Radial artery waveforms, calibrated to brachial BP, were measured by planation tonometry and the SphygmoCor apparatus, as described previously.12 The radial augmentation index (Alx) was derived from averaged radial artery waveforms. Aortic Alx, aortic Alx adjusted to a standard HR of 75 bpm, and central aortic BP were calculated from central aortic waveforms, which were derived by applying a generalized transfer function to the directly measured radial waveforms. True mean arterial BP was derived from integration of the radial waveform. The SphygmoCor apparatus was also used to measure carotid-femoral pulse wave velocity (CF-PWV), as described previously.12

Protocol

On each study day, subjects took their usual medicines at home at 7:00 AM before coming to the research center to start the experimental protocol at 8:00 AM. Subjects did not eat until after the study was completed. The subjects were rested in the supine position for 30 minutes, and then BP, HR, pulse wave analysis, and CF-PWV were measured (in that order) 10 minutes and 5 minutes before study drug administration. BP, HR, pulse wave analysis, and CF-PWV were measured at 20-minute intervals for the first hour after drug administration and then at 30-minute intervals to 4 hours. Apart from when the study drugs were administered, the subjects were supine throughout. All of the measures were made in duplicate, and mean values were entered into the analyses. At the end of the study period, the subjects were asked an open question (“did they feel unwell”) to monitor for any adverse symptoms.

On separate visits, 5 days apart, subjects received the following oral study drugs in random order: placebo sildenafil and placebo ISMN; sildenafil 50 mg and ISMN placebo; placebo sildenafil and ISMN 10 mg; and sildenafil 50 mg and ISMN 10 mg. The 2 drugs were ingested with water with the subjects sitting upright. Because the ISMN and ISMN placebo were not matched in terms of size and shape, the subjects’ eyes were covered while receiving the study medicines.

Analysis

The data were analyzed by calculating the area under the curve (AUC) for each parameter over time. Therefore, each subject had a value for the AUC for each study drug combination (placebo, sildenafil alone, ISMN alone, and the combination of sildenafil and ISMN). The AUCs for each study drug combination were compared by paired Student’s t test. The level of nominal significance was P=0.05. Because we performed a number of pairwise comparisons on the AUCs for each parameter, the significance level adjusted for multiple comparisons was P<0.002. The actual P values for each comparison are stated in the Results section and the Figures to clarify the significance of each comparison at both the uncorrected and corrected nominal levels.

Results

Thirteen subjects attended for screening, and 6 were recruited. Of the 7 patients not recruited, 4 had well-controlled BP on ambulatory monitoring, 1 had consistently well-
controlled BP on baseline measurements before study drug administration, 1 did not take part for personal reasons, and another had recently had a minor stroke. None of the subjects had a BP reduction $>/=40$ mm Hg after directly observed therapy. The mean reduction in systolic BP was 22 mm Hg (range: 12 to 35 mm Hg), and diastolic BP was 7 mm Hg (range: $-2$ to $13$ mm Hg). The baseline characteristics are presented in the Table. With regard to safety, the drugs were well tolerated with only 2 subjects experiencing minor adverse effects. One experienced short-lived flushing, headache, and dizziness with the combination of sildenafil and ISMN, and the other a mild headache with sildenafil alone.

The data for brachial BP and mean arterial pressure (MAP) are shown in Figure 1. Sildenafil alone, ISMN alone, and the combination all significantly reduced systolic BP, diastolic BP, and MAP compared with placebo if a nominal significance of $P<0.05$ was used. If the significance level was corrected for multiple comparisons ($P<0.002$), then ISMN alone and combined with sildenafil significantly reduced MAP compared with placebo. The AUCs for systolic BP were as follows: placebo, 1541 (95% CI: 55 to 3027); sildenafil alone, $-1277$ (95% CI: $-2557$ to 4); ISMN alone, $-2118$ (95% CI: $-3818$ to $-419$); and ISMN and sildenafil, $-4127$ (95% CI: $-6325$ to $-1928$). The AUCs for diastolic BP were as follows: placebo, 663 (95% CI: $-271$ to 1598); sildenafil alone, $-1545$ (95% CI: $-2241$ to 849); ISMN alone, $-2143$ (95% CI: $-4171$ to $-114$); and ISMN and sildenafil, $-3238$ (95% CI: $-4528$ to $-1949$). The effects of sildenafil alone and ISMN alone were no different for systolic or diastolic BP, but ISMN caused a greater fall in MAP than sildenafil ($P=0.006$). The combination of sildenafil and ISMN produced a greater fall in systolic BP than either drug.
given alone ($P<0.03$) and a greater fall in diastolic BP ($P=0.02$) and MAP ($P<0.001$) than sildenafil alone. There was no significant difference in diastolic BP or MAP when the combination was compared with ISMN alone.

The data for arterial wave reflection are shown in Figure 2. ISMN alone and in combination with sildenafil significantly reduced arterial wave reflection compared with both placebo and sildenafil alone ($P<0.002$). The effects of sildenafil alone, ISMN alone, and the combination of sildenafil and ISMN on each of aortic AIx, aortic AIx adjusted to a standard HR of 75 bpm, and radial augmentation index showed the same pattern.

The data for central BP are shown in Figure 3. Sildenafil alone, ISMN alone, and the combination all reduced central systolic ($P<0.002$) and diastolic BPs ($P<0.05$ for sildenafil and ISMN alone; $P=0.002$ for combination) compared with placebo. Central systolic BP was reduced more by ISMN alone than by sildenafil alone ($P=0.002$). The combination of sildenafil and ISMN produced a greater fall in central systolic BP than either drug given alone (versus sildenafil: $P=0.003$; versus ISMN: $P=0.03$) and a greater fall in central diastolic BP than sildenafil alone ($P=0.009$). There was no significant effect on HR or CF-PWV with sildenafil alone, ISMN alone, or in combination (data not shown).

**Discussion**

The main findings from the present study are that, in patients with TRH maintained on their usual antihypertensive treatment, both sildenafil and ISMN given alone acutely reduced BP. In this small proof-of-concept study, the combination of sildenafil and ISMN produced additional BP reduction and was well tolerated. After correction of the level of nominal significance for multiple pairwise comparisons, ISMN given alone still significantly reduced BP, and the combination of
sildenafil and ISMN produced additional BP reduction in comparison with sildenafil alone.

The effect of PDE5 inhibition on BP in patients with TRH has not been investigated previously. The observed maximum reduction in BP with sildenafil of \(13/10\) mm Hg compared with placebo would likely be of real clinical benefit if it were sustained with regular treatment. Given that sildenafil alone reduces BP in untreated hypertensives when taken regularly\(^3\) it seems likely that it would also continue to reduce BP with regular treatment in TRH, but this needs to be tested. Once-daily extended-release ISMN has already been shown to reduce systolic BP, but not previously diastolic BP, in patients with treatment-resistant systolic hypertension.\(^13\) In the present study, we confirm the reduction in systolic BP and demonstrate that ISMN also reduces diastolic BP, suggesting that the benefit of organic nitrates may not be restricted to systolic BP when a heterogeneous TRH population is studied. Compared with placebo, ISMN reduced BP acutely to a maximum of \(18/14\) mm Hg, and this was achieved at a very low dose of 10 mg. As with sildenafil, whether this effect can be sustained with regular treatment clearly warrants further investigation. It is interesting that neither drug alone is considered to be a particularly powerful antihypertensive, at least in the doses used, yet clinically significant BP reductions occurred although subjects were treatment resistant. One possible explanation for this is that the NO-cGMP pathway is a new target, little influenced by the usual antihypertensives that the subjects were taking. As a consequence, the potential for BP reduction with drugs that act on this pathway (eg, soluble guanylate cyclase activators\(^14\)) might be greater than with drugs acting on pathways already targeted by other drugs. In this proof-of-concept study, none of the subjects were prescribed an aldosterone receptor antagonist as part of their regular antihypertensive treatment. There is evidence that these agents are effective in patients with TRH,\(^15\) and further studies will be required to determine whether the combination of a PDE5 inhibitor and NO donor produces a larger BP reduction than an aldosterone receptor antagonist.

The primary aim of the present study was to investigate the effect of combined sildenafil and ISMN. There are concerns that this combination could produce excessive BP reduction and unwanted adverse effects. However, we found the combination to be well tolerated in our small group of carefully selected patients with TRH. When given together, these drugs substantially reduced BP, to a maximum of \(26/18\) mm Hg compared with placebo. The effect on systolic BP was greater than the effect of either drug given alone, and the effect on diastolic BP was greater than that of sildenafil alone. Even with the lower value of nominal significance, after correction for multiple comparisons, the combination of sildenafil and ISMN has a significantly larger effect on MAP than sildenafil alone. There was also a trend to a greater reduction in diastolic BP than with ISMN alone, and the lack of statistical
significance may well be attributed to the small size of the study. The effect of the combination on BP was no greater than would be expected from the sum of the effects of each drug given individually, so they cannot be said to be synergistic, but might indicate that they could be safely combined to reduce BP in TRH in a controlled manner. However, although the present study demonstrates the potential of an organic nitrate and PDE5 inhibitor combination to reduce BP in TRH, further research is needed to establish the longer-term efficacy and safety of such an approach.

Although ISMN alone had a slightly greater effect on BP than did sildenafil alone, ISMN substantially reduced arterial wave reflection, whereas sildenafil had little effect on this measure. In addition, there was very little additional effect on wave reflection when sildenafil was given with ISMN. These data suggest that PDE5 inhibitors are not “nitrate-like” in their hemodynamic action, although they act on the same biochemical pathway. Sildenafil alone had a similar effect on central systolic BP (maximum reduction of $\approx 13$ mm Hg versus placebo) as it did on brachial systolic BP (maximum reduction of $\approx 15$ mm Hg versus placebo). In contrast, the effect of ISMN alone on systolic BP was greater centrally (maximum reduction of $\approx 28$ mm Hg versus placebo) than brachially (maximum reduction of $\approx 18$ mm Hg versus placebo). Given that brachial systolic BP was greater than central systolic BP at baseline, the proportional difference in the effect of ISMN between the 2 sites was even larger. There is evidence that reducing central BP may be more important than reducing brachial BP in preventing cardiovascular events. Therefore, the substantial effect of ISMN on central systolic BP in TRH may be of particular benefit if it were sustained with regular treatment. Even further benefit might be gained with the addition of sildenafil, given that the combination reduced central systolic BP by $\approx 36$ mm Hg.

There are limitations to our study. Because we only investigated the acute effects of our study drugs, we cannot comment on whether ISMN tolerance will develop and diminish the impressive BP reductions seen with a single dose. Our studies were performed with the subjects supine. Whether the combination of sildenafil and ISMN would be as well tolerated in ambulant patients is unknown. This study is a small proof-of-concept study of carefully selected subjects with single drug doses, but the data generated are compelling as an argument for further studies. Now we need to perform a study of longer duration with larger patient numbers, using a longer-acting PDE5 inhibitor and measuring erect, supine, and ambulatory BPs.

**Perspectives**

Patients with treatment-resistant hypertension present clinicians with a significant therapeutic challenge. In this study we demonstrated that the combination of a PDE5 inhibitor and NO donor produces a clinically significant BP reduction without producing significant adverse effects. The next step is to perform a larger study in ambulatory patients over a longer time course. If the BP reduction that we measured in this proof-of-concept study is maintained, then the combination of a PDE5 inhibitor and NO donor may offer an effective new therapeutic approach to a group of patients with significant clinical need.

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**Disclosures**

None.

**References**


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An erratum has been published regarding this article. Please see the attached page for:
/content/60/1/e8.full.pdf
Correction

In the Hypertension article by Oliver et al (Oliver JJ, Dear JW, Webb DJ. Clinical Potential of Combined Organic Nitrate and Phosphodiesterase Type 5 Inhibitor in Treatment-Resistant Hypertension. Hypertension. 2010;56:62–67), a correction was needed.

Dr Victoria Eleanor Crozier Hughes was erroneously omitted from the author line of the article. She made significant contributions to the design of the study, to recruiting the subjects, and to writing up the work, and presented it at scientific meetings in the United Kingdom.

The corrected author line and affiliations are as follows:

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The other authors apologize for this error.

This correction has been made to the current online version of the article, which is available at http://hyper.ahajournals.org/content/56/1/62.full.