I$_1$-Imidazoline Agonist Moxonidine Decreases Sympathetic Nerve Activity and Blood Pressure in Hypertensives

René Roland Wenzel, Lukas Spieker, Su Qui, Sidney Shaw, Thomas Felix Lüscher, Georg Noll

Abstract—Moxonidine is an I$_1$-imidazoline receptor agonist that reduces blood pressure in hypertensives. Experimental data suggest that moxonidine inhibits central sympathetic activity. However, whether such a mechanism is involved in vivo in humans is still unclear. We investigated the effects of 0.4 mg moxonidine orally on muscle sympathetic nerve activity and heart rate in an open study in 8 healthy volunteers. Furthermore, we studied the effects of 0.4 mg moxonidine on muscle sympathetic nerve activity, heart rate, blood pressure, 24-hour blood pressure profile, and hormone plasma levels in 25 untreated hypertensives in a double-blind, placebo-controlled study. Moxonidine decreased muscle sympathetic nerve activity in both healthy volunteers (P<0.05 versus baseline) and hypertensives (P<0.02 versus placebo). Plasma norepinephrine also decreased (P<0.01), whereas plasma epinephrine and renin levels did not change (P=NS). Furthermore, moxonidine decreased systolic (P<0.0001) and diastolic (P<0.001) blood pressure. Heart rate decreased after moxonidine in healthy subjects (P<0.05); in hypertensives, heart rate decreased during the night hours (P<0.05) but not during daytime (P=NS). Plasma levels of LDL, HDL, and total cholesterol were not influenced by the drug (P=NS). Moxonidine decreases systolic and diastolic blood pressure by inhibiting central nervous sympathetic activity. This makes this new drug suitable for the treatment of human hypertension and possibly for other cardiovascular diseases with increased sympathetic nerve activity, ie, ischemic heart disease and heart failure.

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Key Words: moxonidine ■ sympathetic nervous system ■ hypertension, essential ■ renin ■ norepinephrine

Essential hypertension is thought to be associated with an enhanced sympathetic activity triggered at the level of the central nervous system (CNS) in a complex manner. Therefore, it seems logical to blunt the neuronal centers and pathways involved in the regulation of sympathetic activation at the level of the CNS. Centrally acting antihypertensive drugs such as clonidine, guanfacine, and a-methyldopa have been widely used in the past as effective antihypertensive drugs. However, because of their unpleasant side effects these drugs are no longer used as first-line therapy in hypertension.

Recently, imidazoline receptors in the CNS have been identified; their stimulation (predominantly located in the rostroventrolateral medulla) leads to peripheral sympathoinhibition. Stimulation of imidazoline receptors seems to induce effects similar to those induced by stimulation of central a$_2$-adrenergceptors; however, the pattern of adverse reactions seems to be more favorable. The newly developed central antihypertensives, ie, moxonidine and rilmenidine, act mainly on imidazoline-1 receptors and less so on central a$_2$-adrenergceptors in an agonistic fashion. Indeed, affinity of moxonidine and rilmenidine for imidazoline-1 receptors is higher than that of clonidine; in contrast, other centrally acting antihypertensives, ie, a-methyldopa, guanfacine, or guanabenz, act mainly on central a$_2$-receptors.

Moxonidine effectively reduces blood pressure; however, side effects such as dizziness and dry mouth are much less than with the older centrally acting antihypertensives, ie, clonidine. Indeed, these side effects seem to be due to activation of central a$_2$-receptors. Moxonidine, however, stimulates the imidazoline-1 receptors in the ventrolateral area of the medulla oblongata, which, at least in animals, leads to a decreased sympathetic tone in resistance vessels, the heart, and the kidney. Although application of moxonidine reduces plasma catecholamines and plasma renin in hypertension, no data with direct measurement of sympathetic outflow in humans under in vivo conditions are available thus far.

Microneurography allows direct monitoring of muscle sympathetic nerve activity (MSA). The signals can be obtained on-line, and therefore small and short-lasting changes during stimulatory maneuvers as well as their time course can also be recorded. Most importantly, this methodology directly assesses electric outflow of the sympathetic nervous system (SNS) from the medulla oblongata, while the more widely used plasma catecholamine levels only reflect the overflow of the adrenergic neurotransmitters from the synaptic cleft and therefore give only an indirect estimate of MSA. Although plasma norepinephrine levels correlate to...
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Informed consent was obtained from all subjects. The study was approved by the ethical committee of the University Hospital Inselspital, Bern, Switzerland. In the hypertensive study, the significance of differences were calculated by ANCOVA (1-sided, 5% CIs); a P value of ≤0.05 was considered statistically significant. For the comparison between hypertensives and normotensives, an unpaired t test was performed. 

Microneurography

Multifiber recordings of MSA were obtained from the peroneal nerve with tungsten microelectrodes as described. A reference electrode was inserted subcutaneously 1 to 2 cm from the recording electrode. MSA was amplified, filtered, and integrated. The signal was displayed on an oscilloscope and registered on a thermocoupled printer. In addition, the signal was digitized (A/D card MIO 16L, National Instruments) and recorded on a computer (Apple Macintosh Power PC) with a sampling rate of 1500 Hz.

ECG and Blood Pressure

An ECG was recorded simultaneously throughout the entire experiment. Blood pressure was assessed noninvasively with an oscillometric occlusion device (Dinamap).

Drugs

Moxonidine (0.4 mg orally) or placebo was supplied and blinded by the company in a neutral capsule.

Plasma Levels of Drug and Hormones and Safety Parameters

Moxonidine plasma levels were determined in human plasma as described. Plasma catecholamines and renin were determined by high-performance liquid chromatography as described. Safety laboratory parameters (hemoglobin, hematocrit, white blood cell count, platelet count, total cholesterol, LDL and HDL cholesterol, creatinine, liver enzymes, and bilirubin) were drawn 7 days before the study and after the study in all patients.

Analysis and Statistics

Data are given as mean±SEM. In the pilot study with healthy subjects, an ANOVA for repeated measures was performed (95% CIs). In the hypertensives study, the significance of differences were calculated by ANCOVA (1-sided, 5% CIs); a P value of ≤0.05 was considered statistically significant. For the comparison between hypertensives and normotensives, an unpaired t test was performed. Normal distribution of residuals, comparable variances between treatments, and homogeneity of regression slopes were checked to justify the model.

### Methods

#### Study Population

In part 1 of the study, a group of 8 young healthy subjects was investigated (age, 26±1 years, P<0.05 versus hypertensives; sex, 7:1 [male:female]; body mass index, 22.3±2, P<0.05 versus hypertensives). In part 2 of the study, 26 patients with untreated arterial hypertension were studied in a double-blind, placebo-controlled design (Table 1). Hypertensives were either patients with newly diagnosed hypertension and/or without prior antihypertensive treatment or previously treated patients with known hypertension (Table 1); in the latter case, treatment was stopped 2 to 4 weeks depending on the plasma half-life (in the case of β-blockers, 4 weeks in any case) before the start of the study. The subjects were free of any cardiovascular diseases other than hypertension on the basis of the medical history and a physical examination before the study. Written informed consent was obtained from all subjects. The study was approved by the ethical committee of the University Hospital Inselspital, Bern, Switzerland.

#### Experimental Protocol

The study consisted of 2 parts. Part 1 investigated (age, 26±1 years, P<0.05 versus hypertensives; sex, 7:1 [male:female]; body mass index, 22.3±2, P<0.05 versus hypertensives). Part 2 consisted of a double-blind, placebo-controlled study with 0.4 mg moxonidine or placebo in untreated hypertensives. The protocol was a parallel group design with single administration of either placebo or 0.4 mg moxonidine orally. Patients were randomized to either moxonidine or placebo according to a randomization code provided by the manufacturer. If patients had been previously treated for hypertension, any antihypertensive drug was discontinued 2 to 4 weeks depending on the plasma half-life (in the case of β-blockers, 4 weeks in any case) before the start of the study.

During the run-in period, ie, 7 days before drug administration, a 24-hour blood pressure recording (Spacelabs) was made, and blood samples for laboratory testing were drawn in the hypertensive patients; 24-hour blood pressure recording was repeated on study day at 9 AM, ie, 1 hour before drug administration. Patients did not receive any cardiovascular drugs except the study medication during the entire study period.

On study day, all subjects were studied under the same conditions, ie, in the morning (9 AM), after a light breakfast. After micturition to avoid any stimulation of MSA through bladder distension, subjects were asked to resume the supine position. The left or right leg was fixed by a vacuum cushion, and ECG, blood pressure cuff, and respiration strain gauge were fixed. After the microelectrode was placed for MSA recording, a catheter (Venflon, Ohmeda) was inserted into a cubital vein. Thirty minutes after puncture of the vein, baseline recordings, including blood samplings, were performed, and MSA was assessed for 30 minutes. Then either placebo or 0.4 mg moxonidine (blinded capsules) was administered orally. MSA and the other hemodynamic parameters were assessed continuously during the baseline measurements and until 150 minutes after drug administration. When changes of the electrode position occurred, the experiment was discarded. Blood samples for catecholamines, renin, and moxonidine plasma levels were obtained at baseline and 30, 60, 90, 120, and 150 minutes after drug administration. Twenty-four-hour blood pressure measurement was continued until the next morning at 9 AM. We chose the period of 150 minutes after drug administration on the basis of previously published literature on the pharmacokinetics and pharmacodynamics of moxonidine as well as on the basis of our own previous experience, including pilot studies in healthy volunteers, which showed a significant effect of moxonidine on MSA after 60 to 120 minutes.

#### Table 1: Major Demographic Data for Hypertensive Subjects

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=12)</th>
<th>Moxonidine (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.5±9</td>
<td>55.2±7</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>11:1</td>
<td>11:3</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.3±3</td>
<td>26.8±4</td>
</tr>
<tr>
<td>Baseline heart rate, bpm</td>
<td>79±2</td>
<td>75±3</td>
</tr>
<tr>
<td>Baseline blood pressure, mm Hg</td>
<td>152±4/91±2</td>
<td>153±3/95±2</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>Previous antihypertensive treatment, %</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>β-blockers</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td>Diuretics</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>Other</td>
<td>43</td>
<td>37</td>
</tr>
</tbody>
</table>

Antihypertensive treatment was stopped 2 to 4 weeks before the study began (for details, see text).

A certain degree with MSA, plasma catecholamines reflect not only the activity of adrenergic neurons but also that of the adrenal medulla. Finally, most methodologies to measure plasma catecholamines are prone to considerable variation.

Therefore, we investigated the effects of moxonidine on MSA (1) in normotensive healthy volunteers in an open pilot study and (2) in untreated hypertensive patients in a double-blind, randomized, placebo-controlled study.

## Experimental Protocol

The study consisted of 2 parts. Part 1 investigated the effects of 0.4 mg moxonidine in young healthy volunteers in an open design. Part 2 consisted of a double-blind, placebo-controlled study with 0.4 mg moxonidine or placebo in untreated hypertensives. The protocol was a parallel group design with single administration of either placebo or 0.4 mg moxonidine orally. Patients were randomized to either moxonidine or placebo according to a randomization code provided by the manufacturer. If patients had been previously treated for hypertension, any antihypertensive drug was discontinued 2 to 4 weeks before the study began.

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Results

Muscle Sympathetic Nerve Activity

Healthy Volunteers
Baseline MSA was 33 ± 4 bursts/min (cumulative amplitude, 15 ± 3 [arbitrary units]). Both burst count (Figure 1, left panel) and cumulative burst amplitude (Figure 1, right panel) decreased significantly 150 minutes after drug ingestion (P < 0.05 versus baseline).

Hypertensives
Baseline MSA was similar in the placebo (46 ± 4 bursts/min; 19 ± 3 cumulative amplitude [arbitrary units]) and the moxonidine groups (43 ± 3 bursts/min; 19 ± 3 cumulative amplitude [arbitrary units]; P = NS versus placebo) but significantly higher compared with the healthy volunteers (P < 0.05). One hundred fifty minutes after ingestion of the drug, cumulative amplitude of MSA increased in the placebo group but decreased in the moxonidine group (Figures 1 [right panel] and 2; P < 0.02 versus placebo). MSA, expressed as bursts per minute, tended to decrease in the moxonidine group compared with placebo; however, the difference did not reach statistical significance (Figure 1, left panel).

Blood Pressure

Healthy Volunteers
Baseline blood pressure in healthy volunteers was 128 ± 4/70 ± 3 mm Hg. Both systolic (from 128 ± 4 to 120 ± 4 mm Hg; P < 0.001) and diastolic (from 70 ± 3 to 64 ± 4 mm Hg; P < 0.001) blood pressure decreased significantly 150 minutes after ingestion of moxonidine.

Hypertensives
Blood pressure was similar under baseline conditions in the placebo and the moxonidine groups (Table 1; P = NS) but was significantly higher than in the healthy volunteers (P < 0.05). One hundred fifty minutes after drug ingestion, both systolic and diastolic blood pressure decreased significantly in the moxonidine group (systolic, -10 ± 4 mm Hg; P < 0.0001 versus placebo; diastolic, -5 ± 2 mm Hg; P < 0.001 versus placebo), whereas it did not change in the placebo group (systolic, +2 ± 2 mm Hg; P = NS versus baseline; diastolic, +1 ± 2 mm Hg; P = NS versus baseline). Furthermore, moxonidine significantly decreased both systolic (P < 0.01) and diastolic (P < 0.02) 24-hour blood pressure profiles, whereas placebo had no effect (Figure 3).

Heart Rate

Healthy Volunteers
Heart rate at baseline was 64 ± 2 bpm and decreased significantly 150 minutes after ingestion of moxonidine (from 64 ± 2 to 60 ± 3 bpm; P < 0.05 versus baseline).

Hypertensives
Baseline heart rate was similar in both groups (Table 1; P = NS) but was significantly higher than in the healthy volunteers (P < 0.05 versus healthy volunteers). One hundred fifty minutes after ingestion of moxonidine or placebo, heart rate did not change significantly (placebo, -0.6 ± 2 bpm; moxonidine, -2 ± 2 bpm; P = NS versus placebo). However, 24-hour heart rate profile derived from the 24-hour blood pressure measurements revealed a significant decrease in heart rate after moxonidine during the nighttime but not during daytime (Figure 4; P < 0.05 versus placebo), whereas placebo had no effect (P = NS).
Blood Chemistry

Plasma Catecholamines

Healthy Volunteers
Plasma norepinephrine decreased from 946 ± 118 to 709 ± 413 pmol/L (P < 0.01). Plasma epinephrine values did not change (P = NS).

Hypertensives
Baseline epinephrine and norepinephrine values were not significantly different, although they tended to be slightly higher in the moxonidine group (P = NS versus placebo). After moxonidine, plasma norepinephrine decreased significantly (Table 2), whereas it did not change after placebo. Plasma epinephrine did not change either after placebo or after moxonidine (Table 2).

Plasma Renin
There were no changes in plasma renin activity in the hypertensives either after placebo or after moxonidine (Table 2; P = NS versus placebo).

Moxonidine Plasma Levels
In hypertensives receiving moxonidine, plasma levels of the drug increased significantly (Figure 5; P < 0.0001). Peak plasma levels were achieved 60 minutes after intake (2244 ± 450 pg/mL). Effects of moxonidine on blood pressure and MSA did not correlate with the plasma levels of the drug (r = 0.04 to 0.1; P = NS).

Safety Parameters
There were no changes in hemoglobin, hematocrit, white blood cell count, platelet count, total cholesterol, LDL or HDL cholesterol, creatinine, liver enzymes, or bilirubin after placebo or moxonidine (P = NS).

Discussion

The present double-blind, placebo-controlled study demonstrates for the first time that the I1-imidazoline receptor agonist moxonidine reduces blood pressure in untreated hypertensive subjects through a reduction in central sympathetic outflow. Indeed, with the use of microneurography, a significant reduction in MSA up to 150 minutes after ingestion of 0.4 mg moxonidine orally in both untreated hypertensives and young healthy volunteers was observed. Furthermore, plasma norepinephrine levels decreased significantly after moxonidine. Interestingly, heart rate decreased during the nighttime but not during the daytime.

The SNS is an important regulator of the circulation and the heart. Although its role in advanced hypertension is controversial, the SNS seems to contribute to the development of hypertension in early stages of the disease.1,23 Furthermore, SNS activity increases with age independently of any disease state.2 In congestive heart failure SNS activity is markedly elevated and strongly correlates with mortality of the patients.26,27

Moxonidine is an I1-imidazoline receptor agonist that acts on I1-imidazoline receptors in the ventrolateral medulla. When applied in dosages equipotent to clonidine, its side effects, ie, dry mouth and dizziness, are less pronounced than with the α2-receptor agonist clonidine.5,10 After oral application (0.2 mg), peak plasma concentrations of moxonidine are achieved within <1 hour, with a half-life of 2 hours.20 In the present study we used 0.4 mg moxonidine, which is a well-established, effective dose to treat mild to moderate hypertension.10,11 In this study peak plasma levels were achieved within 60 minutes after drug intake in the moxonidine group and slightly decreased during the observation period of 150 minutes. However, plasma levels might not necessarily reflect the effects of moxonidine in the CNS because the drug diffuses to a significant degree into the third compartment, including the brain tissue.

Under our experimental conditions, we observed an increase in MSA in the placebo group. This is in agreement with previous studies; most likely, the study design leads to a certain discomfort of the patients, which increases MSA somewhat. Furthermore, it is well known that plasma volume
Moxonidine Decreases Sympathetic Nerve Activity in Hypertensives

TABLE 2. Effects of Moxonidine or Placebo on Plasma Levels of Hormones and Drug Plasma Levels in Untreated Hypertensive Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Placebo</th>
<th>150 min After Placebo</th>
<th>Baseline Moxonidine</th>
<th>150 min After Moxonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine, pmol/L</td>
<td>2177±323</td>
<td>2001±184</td>
<td>3092±670</td>
<td>2148±160*</td>
</tr>
<tr>
<td>Epinephrine, pmol/L</td>
<td>371±59</td>
<td>334±49</td>
<td>306±48</td>
<td>292±43</td>
</tr>
<tr>
<td>Renin, ng/mL</td>
<td>0.7±0.2</td>
<td>0.6±0.1</td>
<td>0.5±0.1</td>
<td>0.4±0.1</td>
</tr>
<tr>
<td>Moxonidine plasma levels, pg/mL</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1598±260*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *P<0.001 vs placebo.

decreases, since there was no fluid substitution during the experiment. This decrease in central venous pressure may also contribute to the slight increase in SNS activity during the study period. Moxonidine significantly reduced MSA compared with placebo. This demonstrates that the observed reduction in blood pressure is mainly due to a central inhibitory effect of moxonidine on the SNS. Effects of moxonidine on burst count of MSA were more pronounced in healthy volunteers than in hypertensives; this is due to the fact that in young, lean normotensives, burst amplitude is small; thus, when MSA decreases, a certain amount of bursts disappears. In contrast, in the elder hypertensive patients, burst amplitude is much higher; therefore, a reduction in MSA markedly reduces burst amplitude but not burst count. Thus, burst amplitude is a more valid and reliable parameter for MSA, especially in subjects with high sympathetic activity. Indeed, moxonidine significantly decreased burst amplitude in both normotensive and hypertensive subjects to a similar degree, whereas in the placebo group there was an increase in MSA. Plasma norepinephrine levels decreased in parallel after administration of moxonidine. Since moxonidine experimentally also stimulates presynaptic a2-receptors, decreases of plasma norepinephrine may also be due to this phenomenon in part.28 Furthermore, moxonidine might stimulate renal sodium excretion, thus contributing to a blood pressure reduction.29 The present study design does not allow discrimination between the central and the peripheral effects of the drug. There were no significant changes in plasma renin activity. This is in contrast to other studies showing a decrease in plasma renin.11,12 However, patients were in the supine position during the sampling of renin plasma levels. Therefore, baseline renin activity was already low and could not be further suppressed by moxonidine.

Plasma levels of the drug did not correlate with changes in MSA or blood pressure. Indeed, significant drug plasma levels were already achieved within 60 minutes after administration of moxonidine, with the maximum after 120 minutes; in contrast, the effects of moxonidine on MSA and blood pressure were maximal 150 minutes after drug administration and beyond. Thus, plasma levels are not an indicator of drug effects. This is in agreement with previous studies on the pharmacodynamic action of moxonidine and can be explained by the fact that the drug rapidly diffuses into the CNS, where it exerts its sympatholytic effects.12,20

In hypertensives, heart rate decreased only during nighttime as assessed by the 24-hour blood pressure recordings. The decrease in heart rate observed during nighttime further indicates a sympatholytic effect; this might be beneficial in hypertensives with ischemic heart disease, since ischemic events are known to occur preferentially in the early morning hours, when sympathetic activity is high. In contrast, in the young healthy volunteers there was a significant decrease in heart rate after moxonidine. The reasons for these findings are unclear; possibly vagal activity is higher in young healthy volunteers than in elderly hypertensives and might have been unmasked with a sympatholytic agent. Indeed, in patients with hypertension or with congestive heart failure, parasympathetic activity is impaired.30,31

Heart failure is an important complication of hypertension. SNS activity is high in those patients and correlates with mortality.27 Thus, an antihypertensive drug that decreases SNS activity might be preferable, particularly in these patients. Indeed, in a first study with moxonidine in congestive heart failure, the drug decreased heart rate and plasma norepinephrine levels and performed well in terms of its tolerability.32

In summary, moxonidine reduces blood pressure mainly through a reduction of MSA in both normotensive and hypertensive subjects. This mechanism of action might be beneficial in hypertensives with elevated sympathetic tone, especially in the presence of concomitant cardiovascular diseases, ie, ischemic heart disease and/or congestive heart failure.

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