Efficacy of moxonidine in the treatment of hypertension in obese, noncontrolled hypertensive patients

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Efficacy of moxonidine in the treatment of hypertension in obese, noncontrolled hypertensive patients.

Background. Obesity has become an epidemic problem, contributing to metabolic syndrome, type 2 diabetes, hypertension, and cardiovascular disease. An adequate blood pressure control in this population of obese individuals is extremely difficult to achieve, and in most cases, therapeutic combinations are required. Pharmacologic treatment with moxonidine, a central I1 imidazole receptor agonist, is a very interesting option because it acts upon the mechanisms implicated in the development of arterial hypertension in these patients. In addition, the drug improves the peripheral insulin resistance often found in obese patients, which contributes to maintain high blood pressure.

Methods. An interventional study has been designed, adding moxonidine to noncontrolled hypertensive, obese subjects in whom a hypocaloric diet was previously recommended. A total of 25 primary care centers participated in the study, with a total of 135 patients recruited.

Results. One hundred twelve patients were included in the study; 25 of them had type 2 diabetes. The mean reduction in systolic and diastolic blood pressure after 6 months treatment with moxonidine was 23.0 and 12.9 mm Hg, respectively. The mean systolic and diastolic pressures were 158.5 ± 10.6 and 95.1 ± 9 mm Hg, respectively, at baseline, versus 135.5 ± 11.5 and 82.2 ± 5.8 mm Hg at the end of the study. Creatinine clearance was significantly decreased in hyperfiltrating obese patients (143.6 ± 31 vs. 128.2 ± 27.9, P < 0.0001), without any significant change in patients with normal or slightly decreased renal function (81.9 ± 18.9 vs. 80.9 ± 17.5). Only 8 mild adverse reactions in 7 patients were recorded during the study.

Conclusion. Moxonidine is useful and safe for controlling arterial hypertension in obese patients.

Obesity shows an increased cardiovascular risk because it is associated with the development of type 2 diabetes and dyslipidemia [1, 2]. Of the different anthropomorphic types of obesity, the android presentation is the most deleterious one, from the cardiovascular view. This type of obesity is characterized by increased visceral fat, with a waist/hip index above 0.95 and 0.85 in males and females, respectively. Obesity increases both cardiovascular morbidity-mortality and health care costs. It has been estimated that an increase of 1 kg in body weight implies a 3.1% rise in global cardiovascular risk.

An increase in body mass index (BMI) is correlated to increased insulin resistance. In fact, increased body weight (BW) is a risk factor for the development of type 2 diabetes [3–5]. The association of obesity, diabetes, and hypertension is highly prevalent, and increases with age. Epidemiologic studies indicate that after 50 years of age, this triple association is relatively frequent. These processes are, in turn, characterized by underlying hyperinsulinism and resistance to the peripheral action of insulin—this constituting a common etiopathogenic factor that facilitates the expression of these associated pathologic processes.

Obesity alters renal function in addition to causing hypertension [6, 7]. Among the different mechanisms implicated should be mentioned the insulin resistance and hyperinsulinism generated, activation of the renin-angiotensin system and sympathetic nervous system, as well as intrarenal alterations. Different evidence has shown that blocking the renin-angiotensin-aldosterone system is a benefit for this obese hypertensive population, similar to the selective alpha- and beta-adrenergic block. Numerous studies have analyzed the role of leptin in the activation of the sympathetic nervous system in such individuals. It is known that obesity favors an increase in intraglomerular pressure, resulting in hyperfiltration, glomerular damage, sodium retention, and increased arterial pressure.

Of the different factors that associate arterial hypertension and obesity, peripheral insulin resistance and hyperinsulinism, which are often found in obesity, should be mentioned. It has been suggested that insulin resistance and hyperinsulinism constitute the etiopathogenic link between obesity and arterial hypertension. Both of these factors favor metabolic alterations, which in turn increase cardiovascular risk. From the pathogenic

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perspective, and in addition to the above factors, the development of hypertension in obese patients seems to be mediated by other mechanisms that alter renal function—with chronic increments in tubular sodium reabsorption and displacement of the natriuresis/pressure curve, increased sympathetic and renin-angiotensin system activity, among other phenomena.

Pharmacologic treatment with moxonidine, a central \text{I}_1 imidazole receptor agonist, is a very interesting option because it acts upon the mechanisms implicated in the development of arterial hypertension in these patients [1, 2, 8]. In addition, the drug improves the peripheral insulin resistance often found in obese patients, which contributes to maintain high blood pressure [9, 10].

METHODS

An open, multicenter observational study was designed in the primary care setting to assess the effects of moxonidine on a subset of obese and hypertensive individuals not adequately controlled with their standard antihypertensive treatment. An evaluation was performed, analyzing the blood pressure control achieved after the association of moxonidine to their previous treatment. At the end of the study, patients were considered as BP controlled if BP was \(<140/90\) mm Hg in nondiabetic patients and \(<130/85\) mm Hg in diabetics [12]. The tolerance of the drug and the possible repercussions upon renal function were also analyzed.

The study included obese hypertensive patients aged 18 to 80 years who gave informed consent to participation and met the following inclusion criteria: (1) prior treatment with antihypertensive medication, although without adequate control [systolic blood pressure (SBP) 140–179 mm Hg and/or diastolic blood pressure (DBP) 90–109 mm Hg]. In the case of diabetic hypertensive individuals previously treated with antihypertensive drugs, the requirements were SBP 130 to 179 mm Hg and/or DBP 85 to 109 mm Hg; and (2) overweight-obese status as defined by BMI \(\geq 27.5\) and <40.

The following exclusion criteria were established: secondary hypertension, acute myocardial infarction in the previous 6 months, arrhythmias, unstable angina, heart failure (left ventricle ejection fraction \(<40\%\) ), cerebrovascular events in the preceding year, liver failure (hepatic transaminase levels more than 2-fold the baseline values), women of fertile age failing to adopt adequate contraceptive measures, and bedridden patients or individuals with incapacitating illnesses.

Blood pressure was measured according to internationally accepted guidelines [11, 12]. Blood pressure was determined in the dominant arm of the patient, in the sitting position, and after a 5-minute rest period, early in the morning. Three valid recordings were obtained spaced at least 3 minutes apart. The pressure value corresponding to the visit was taken to be the arithmetic mean of the SBP and DBP values. The patients were weighed, and body height was measured without shoes and wearing only light clothing. The BMI was also calculated \([\text{weight in kg/(height in m)}^2]\).

In all cases, moxonidine 0.4 mg was added to the habitual antihypertensive medication to control blood pressure. The drug was administered early in the morning for 6 months, and a hypocaloric (1200 calorie) diet was prescribed together with regular daily exercise (walking for half an hour). Monthly clinical controls were carried out.

Two biochemical controls were done: one before the active treatment period, and the second at the end of the study—including the evaluation of renal function. Glomerular filtration rate (GFR) was assessed by the Cockroft and Gault formula. Patients who had GFR higher than 125 mL/min in men, and higher than 100 mL/min in women were classified as hyperfiltrating. Safety was evaluated by recording the adverse reactions either spontaneously reported by the patient or detected by the investigator, and which appeared or worsened in the course of the study. Safety was also assessed according to evolution of the laboratory test parameters.

A clinical database (Microsoft Excel 97; Microsoft, Redmond, WA, USA) was established for the statistical study, with internal coherence rules and ranges to detect incorrections in the data tables. The SPSS version 11 statistical package was used (Chicago, IL, USA). The continuous variables were described employing central tendency (mean, median) and dispersion measures (standard deviation, minimum, and maximum). The categorical variables were described based on absolute and relative frequency tables. The contrasts and statistical tests employed accepted significance for \(P < 0.05\).

RESULTS

The results obtained were divided into 4 sections: sample characteristics, antihypertensive efficacy analysis, study of renal function, and safety analysis.

Sample characteristics

A total of 112 patients from 135 recruited were finally included in the study (61 males and 51 females), aged 61.2 \(\pm\) 10.6 years, with a height of 161.6 \(\pm\) 8.6 cm. Twenty-five of them had type 2 diabetes. Body weight decreased from 88.19 \(\pm\) 12.09 kg (baseline) to 84.9 \(\pm\) 11.5 kg (6-month) \((P < 0.01)\). BMI decreased from 33.6 \(\pm\) 3.3 kg/m\(^2\) (baseline) to 32.3 \(\pm\) 3.2 kg/m\(^2\) (6-month) \((P < 0.01)\). Baseline waist perimeter was: 111.7 \(\pm\) 14.1 cm, hip perimeter: 110.3 \(\pm\) 13.3 cm, and waist/hip index: 1.0 \(\pm\) 0.1.

The cardiovascular risk factor anamnysis identified hypercholesterolemia in 47.7\% of patients,
tobacco smoking in 27.5%.

Hypertriglyceridemia in 17.4%, diabetes in 22.3%, and tobacco smoking in 27.5%.

**Antihypertensive efficacy analysis**

Because the patients were both obese and hypertensive, a first evaluation will focus on the evolution of blood pressure. The mean decrease in SBP after moxonidine treatment and during the 6-month duration of the study was 23.01 mm Hg (14% of the baseline value). The decrease in DBP was 12.9 mm Hg (13.5% of the baseline value). For the whole group, the mean blood pressure reduction at the end of the study was significantly more marked in the group of nondiabetic (159 ± 12/95 ± 10 vs. 135 ± 10/82 ± 6) than diabetic patients (157 ± 11/95 ± 7 vs. 137.6 ± 12/83 ± 6), P < 0.01.

In terms of blood pressure control, 96 patients (86%) achieved diastolic BP control at the end of the study; 70 (63%) of them had systolic BP adequately controlled, and 54 (48%) were seen to have adequately controlled the 2 BP components after 6 months. A significantly greater percentage of patients who achieved blood pressure control was found among nondiabetics compared with diabetic patients (57% vs. 18%, P < 0.001) (Fig. 2), although the BP control goal demanded by diabetics was more strict (<130/85 mm Hg), than in nondiabetics (140/90 mm Hg). The BMI was also seen to decrease from 33.6 to 32.3 kg/m² (P < 0.01) (Fig. 3).

Associated factors for controlling blood pressure are expressed in Table 1. Only lower baseline glucose levels are significantly related to blood pressure control, expressing that diabetic patients had worse BP control, but the percentage of reduction of the BMI was not significantly related to BP control (Table 1).

The evolution of biochemical parameters is shown in Table 2.

**Study of renal function**

The mean initial and final plasma creatinine levels did not vary (0.96 ± 0.2), but comparing the group of 23 hyperfiltrating patients (GFR >125 mL/min in men and >100 mL/min in women) with those with baseline normal renal function resulted in the following: hyperfiltrating patients had a significantly lower mean plasma creatinine value (0.81 ± 0.2 vs. 1.01 ± 1.8 mg/dL, P < 0.001), which increased at the end of the study to 0.85 ± 0.2 mg/dL. Plasma creatinine did not change over the study in obese patients with normal renal function (1.01 ± 1.8 vs. 0.99 ± 1.9 mg/dL). At the same time, creatinine clearance (Cockcroft-Gault formula) significantly decreased in the whole group (97.3 ± 35.2 to 92.8 ± 30.1, P < 0.001) after 6 months of treatment. However, comparing the 2 groups of patients in relation to GFR, this decrement in the mean GFR was only significant in the group of hyperfiltrating obese patients (N = 23) (143.6 ± 31 vs. 128.2 ± 27.9, P < 0.0001), without any significant change in those obese patients with normal or slightly decreased renal function (81.9 ± 18.9 vs. 80.9 ± 17.5), although hyperfiltrating patients were more obese (98.8 ± 14 vs. 85.1 ± 11 kg, P < 0.001). The percent of reduction in body weight at the end of the study was not significantly different between hyperfiltrating and nonhyperfiltrating obese patients (3.7% vs. 3.3% BW reduction, respectively).
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Table 1. Associated factors in relation to BP control

<table>
<thead>
<tr>
<th></th>
<th>Noncontrolled</th>
<th>Controlled</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age years (years)</td>
<td>61.69</td>
<td>10.97</td>
<td>60.14</td>
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<tr>
<td>Body weight baseline (kg)</td>
<td>88.81</td>
<td>12.82</td>
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<tr>
<td>BMI baseline (kg/m²)</td>
<td>33.67</td>
<td>3.42</td>
<td>33.35</td>
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<tr>
<td>BMI reduction at 6 months (%)</td>
<td>3.32</td>
<td>3.63</td>
<td>4.26</td>
</tr>
<tr>
<td>Glucose baseline (mg/dL)</td>
<td>123.16</td>
<td>35.73</td>
<td>106.3</td>
</tr>
<tr>
<td>Glucose 6 months (mg/dL)</td>
<td>112.53</td>
<td>19.38</td>
<td>99.4</td>
</tr>
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</table>

aMann-Whitney U test.

Table 2. Biochemical data at baseline and at the end of the study

<table>
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<th></th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Min.</th>
<th>Max.</th>
<th>P valuea</th>
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<tbody>
<tr>
<td>Glucose baseline (mg/dL)</td>
<td>109.48</td>
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<td>27.67</td>
<td>70.00</td>
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<tr>
<td>Glucose 6 months (mg/dL)</td>
<td>103.17</td>
<td>99.00</td>
<td>23.04</td>
<td>68.00</td>
<td>187.00</td>
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<tr>
<td>Cholesterol baseline (mg/dL)</td>
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<td>223.00</td>
<td>36.65</td>
<td>130.00</td>
<td>305.00</td>
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</tr>
<tr>
<td>Cholesterol 6 months (mg/dL)</td>
<td>210.14</td>
<td>207.50</td>
<td>25.58</td>
<td>151.00</td>
<td>293.00</td>
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<td>145.50</td>
<td>75.92</td>
<td>32.00</td>
<td>459.00</td>
<td></td>
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<tr>
<td>Triglycerides 6 months (mg/dL)</td>
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<td>136.50</td>
<td>88.09</td>
<td>47.00</td>
<td>842.00</td>
<td>0.0016</td>
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<tr>
<td>HDL-cholesterol baseline (mg/dL)</td>
<td>50.22</td>
<td>48.00</td>
<td>11.60</td>
<td>28.40</td>
<td>90.00</td>
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<tr>
<td>HDL-cholesterol 6 months (mg/dL)</td>
<td>50.72</td>
<td>48.00</td>
<td>10.33</td>
<td>31.60</td>
<td>77.00</td>
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<tr>
<td>Creatinine baseline (mg/dL)</td>
<td>0.96</td>
<td>0.93</td>
<td>0.20</td>
<td>0.50</td>
<td>1.87</td>
<td>0.5053</td>
</tr>
<tr>
<td>Creatinine 6 months (mg/dL)</td>
<td>0.96</td>
<td>0.90</td>
<td>0.19</td>
<td>0.60</td>
<td>1.82</td>
<td></td>
</tr>
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</table>

aWilcoxon test.

Safety analysis

Only 8 adverse reactions were recorded in 7 patients [knee pain, dizziness, drowsiness (3 cases), dry mouth, and slight worsening of chronic obstructive lung disease.

DISCUSSION

The present study demonstrates the efficacy of moxonidine for the control of arterial hypertension associated with obesity, even in diabetic patients. An adequate blood pressure control in this population of obese individuals, particularly diabetics, is extremely difficult to achieve, and in most cases therapeutic combinations are required. The special mechanism of action of moxonidine [13–16], reducing sympathetic activity [17–19] and improving insulin sensitivity [20], may account for the increased antihypertensive efficacy in this population [21–23]. Thus, moxonidine is particularly useful in cases of arterial hypertension associated with metabolic syndromes [24–30].

On the other hand, the results obtained in this study indicate that hyperfiltrating patients, as a result of hypocaloric diet plus moxonidine treatment and BP control, have decreased glomerular filtration rate (GFR) to near normal values, but GFR is not altered in those patients with normal or slightly reduced GFR [31–36]. These changes seen in creatinine clearance could also be explained at least in part by the reduction of body weight. GFR was estimated by the Cockcroft-Gault formula; however, the body weight reduction was similar in both groups of high and normal GFR.

As a comparison of our results with those of other authors, Haenni et al [3] investigated whether insulin sensitivity and response are modified by moxonidine treatment in obese patients with primary arterial hypertension. They analyzed 74 hypertensive subjects with BMI >27, and found a 21% increase in insulin sensitivity versus the placebo group. Moreover, no significant side effects were observed. Ernsberger et al [37] also analyzed the influence of moxonidine-induced sympathetic inhibition upon carbohydrate metabolism in genetically obese and hypertensive rats—recording a 71% decrease in hyperinsulinemia, and a 25% reduction of free fatty acids. On the other hand, expression of the beta-subunit of the insulin receptor was seen to increase 19%. Rosen et al [38] concluded that moxonidine action upon the imidazole receptors reduces sympathetic activity and offers beneficial effects at different levels, including blood pressure, insulin resistance, lipid metabolism, and others. Regarding kidney function, Wiecek et al [39] found moxonidine to exert beneficial effects upon the urinary excretion of electrolytes and on renal hemodynamics.

Another important consideration is the safety of the drug because few significant side effects were recorded in our study, which is in agreement with the observations of other authors. In effect, moxonidine is very well tolerated, with few interactions when combined with other drugs.

CONCLUSION

The present study shows that moxonidine associated with hypocaloric diet added to the habitual
antihypertensive regimen is useful and safe for controlling arterial hypertension in obese patients. This antihypertensive regimen corrects hyperfiltration in obese hyperfiltrating patients, but does not produce any changes in renal function in obese hypertensive patients with normal or slightly reduced GFR. Thus, moxonidine should be taken into consideration when treating obese patients with plurimetabolic syndromes.

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