Effects of Sustained-Release Moxonidine, an Imidazoline Agonist, on Plasma Norepinephrine in Patients With Chronic Heart Failure

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Background—In chronic heart failure, sympathetic activation is increased. Moxonidine acts on central nervous system receptors to decrease sympathetic activation. We investigated the dose-response relationship of a new sustained-release (SR) preparation of moxonidine and the plasma concentration of norepinephrine in patients with chronic heart failure.

Methods and Results—A total of 268 patients with chronic heart failure in NYHA functional class II to IV on optimal standard therapy were randomized to placebo or 1 of 5 doses of moxonidine SR: 0.3, 0.6, 0.9, 1.2, or 1.5 mg BID. After a dose-titration phase (7 weeks), patients were followed up for another 12 weeks at their maximally tolerated dose. Blood samples for plasma norepinephrine were collected at baseline and weekly during the initial 7 weeks, at week 19, and at the end of the study. At baseline and 7 and 19 weeks, sampling was also done 4 hours after the dose. After the active phases of the study, plasma norepinephrine was evaluated for an additional 3 days. A marked, statistically significant dose-related decrease in plasma norepinephrine was observed for predose levels as well as 4 hours after the dose at week 19. At the highest dose (1.5 mg BID), the trough reduction in norepinephrine was 52%. These reductions were accompanied by a modest decrease in heart rate, a modest increase in left ventricular ejection fraction, and a dose-related increase in adverse events.

Conclusions—Plasma norepinephrine was markedly reduced in a dose-related manner by moxonidine SR. This reduction was accompanied by evidence of reverse remodeling, but also by an increase in adverse events. (Circulation. 2002;105:1797-1803.)

Key Words: heart failure ■ norepinephrine ■ nervous system, sympathetic ■ drugs

Chronic heart failure is associated with activation of the sympathetic nervous system (SNS) as manifested by increased circulating levels of norepinephrine and increased regional SNS stimulation.1 The degree of activation appears to be a marker for both the severity of the syndrome and the risk of death.2-4 Furthermore, inhibition of cardiac sympathetic activity by β-adrenoceptor antagonism exerts a favorable long-term effect on morbidity and mortality.5-8 These data have thus raised the possibility that SNS activity is not only a marker for the severity of heart failure but also a contributor to its progression.

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An alternative to adrenergic receptor blockade would be central inhibition of SNS activity. Interference with a central mechanism that mediates activation could theoretically inhibit both the cardiac and the peripheral vascular effects of SNS stimulation, both of which might contribute to progression of the syndrome. Another potential advantage of such a site of inhibition is that the degree of blockade can be quantified by monitoring plasma norepinephrine levels and thus individualizing treatment to maintain clinically appropriate levels of antiadrenergic effect. In addition, such central inhibition might be better tolerated than treatment with β-adrenoceptor blockers, which require cautious dose titration and are often associated with adverse early effects in patients with heart failure.

In chronic heart failure, agents acting on central sympathetic outflow, such as the α2-agonist clonidine, have been studied in short-term intravenous and oral studies.9,10 Moxonidine is a selective imidazoline ligand that acts specifically on central nervous system receptors to decrease sympathetic outflow.11 In preclinical studies, the antihypertensive effects of moxonidine appear to correlate with its potency at putative

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brain stem imidazoline sites rather than α2-receptors. In clinical studies with an immediate-release (IR) formulation of moxonidine, moxonidine is an effective treatment for hypertension and is equipotent to clonidine with fewer α2-mediated side effects.

It was recently reported, however, that the pharmacodynamic effects of moxonidine IR in patients with chronic heart failure were suboptimal. The moxonidine sustained-release (SR) formulation was developed to allow higher dosages and more stable blood levels of moxonidine. The aim of the Moxonidine Safety and Efficacy (MOXSE) study was to determine the dose-response relationship of oral moxonidine SR on plasma concentration of norepinephrine during short- and long-term administration in patients with symptomatic chronic heart failure. In addition, tolerability and safety were assessed.

Methods

This was a double-blind, randomized, placebo-controlled, multicenter trial with a 19-week treatment duration in patients with symptomatic chronic heart failure in NYHA functional class II to IV. Forty-nine centers in Europe and the United States participated (see Appendix). Patients with a left ventricular ejection fraction (LVEF) ≤35% as assessed by radionuclide angiography, echocardiography, or angiography and treated with digitalis and/or diuretics were eligible. An ACE inhibitor was required unless intolerance had been demonstrated. The dosage of chronic heart failure medication had to be stable for at least 2 weeks before randomization. Exclusion criteria included myocardial infarction within the previous 90 days, significant valvular obstruction, advanced pulmonary disease, systolic blood pressure <90 mm Hg, or β-blocker use within the previous 30 days. The protocol was approved by the ethics committee at each participating center, and each subject provided written informed consent.

Protocol

After screening and baseline visits, patients were randomly allocated to 1 of 6 treatment arms: placebo or target doses of moxonidine SR of 0.3, 0.6, 0.9, 1.2, or 1.5 mg administered twice daily. Patients randomized to target doses of ≥0.6 mg BID were subrandomized to an initial dose of 0.3 or 0.6 mg BID. The initial dose period of ≥1 week was followed by weekly dose increments of 0.3 mg BID (or placebo if needed) to the target dose. If side effects occurred, the dose could be maintained, reduced, or withdrawn. At baseline and at weekly visits during dose titration, predose blood samples were drawn for measurement of plasma norepinephrine concentration. At baseline and after 7 and 19 weeks, patients were observed for 8 hours in the clinic. Blood samples were drawn before and 4 hours after drug administration for plasma norepinephrine levels. On the basis of experience from a pilot dose-finding study, the 4-hour time point was chosen as the optimal expression of reduction in plasma norepinephrine. To evaluate the presence of rebound effects, plasma norepinephrine was also assessed daily for 3 days after study drug withdrawal at 19 weeks.

Originally, the protocol did not require dose tapering after completion of the 19 weeks of active therapy; however, after observing the signs and symptoms of the first 55 patients during this acute withdrawal phase, the Data Monitoring Board recommended dose tapering to avoid the potential of rebound when moxonidine SR was acutely discontinued. Before the introduction of the dose-tapering phase, all patients entered placebo washout. At the end of the dose-maintenance phase, patients who were receiving study drug doses ≥0.6 mg BID were downtitrated to 0.6 mg BID for 1 week. Patients on ≤0.6 mg BID at the end of dose maintenance were maintained on their current dose for 1 week. After this 1-week period, all patients received placebo for 2 weeks. The first 3 days in this period were evaluated in particular by reexaminations.

All blood samples for assessment of plasma levels of norepinephrine were drawn after 30 minutes of supine rest. Blood was collected in vials containing gluthathione. The plasma samples were promptly placed on ice and centrifuged for 20 minutes. The plasma was frozen and shipped on dry ice to a central laboratory where assays were performed by high-performance liquid chromatography.

A 24-hour Holter recording was performed at baseline, at 19 weeks, and at the end of the washout period. LVEF was assessed at baseline and at 19 weeks by radionuclide angiography in US centers where the test was available.

Possible effects of moxonidine on quality of life and signs and symptoms were assessed by a questionnaire with specific questions aimed at sedation. Worsening heart failure and symptomatic hypertension were evaluated by the clinical judgment of the investigators in the absence of predefined criteria.

Statistical Methods

The analyses included efficacy as well as safety evaluations. The primary efficacy objective was to evaluate the dose-related change in plasma norepinephrine from baseline to 4 hours after the dose at 19 weeks. Assessment of the changes in plasma norepinephrine from baseline to the dose at each visit and 4 hours after the dose at 7 weeks were also evaluated. Variables were compared between placebo and each moxonidine dosage group. Continuous variables were analyzed by use of an ANCOVA model, with fixed effects for the treatment groups and the baseline measurement as the covariate. The model, with treatment as a class variable, was used to analyze the treatment effect. The same model, with treatment as a continuous variable, was used for dose trend. Also, an ANCOVA model with the interaction term “treatment by baseline” and treatment as class variables was used to observe interaction effects.

The linear models used in the efficacy analyses were fitted by use of the type III sums of squares from the general linear models procedure in the SAS Statistical package (version 6.12). All tests of significance for main effects were conducted at a 2-sided level of α=0.05, except for all tests of linear dose trend for plasma norepinephrine, for which 1-sided tests of dose effect were performed.

For the analyses of categorical data, because of the potential effect of baseline NYHA class, the Cochran-Mantel-Haenszel type 1 test with 1 degree of freedom adjusted for baseline NYHA was used. In general, both efficacy and safety data were analyzed with an intent-to-treat approach in which all randomized patients who received ≥1 dose of study drug were included in the analysis.

The sample size was based on the slope of the linear dose trend for the change in plasma norepinephrine concentration from baseline to 4 hours after dose at week 19. A decrease of 100 pg/mL in the moxonidine SR 1.5-mg-BID dose group compared with placebo was considered clinically significant. A between-patient SD of ≈209 pg/mL was previously observed.

With a 1-sided significance level of 5% and a power of 80%, the required total sample size was 237. Approximately 270 patients were to be enrolled, to allow for dropouts.

Results

Three of the 268 randomized patients did not receive any study drug, and they are excluded in this analysis. The patient demographics at baseline for the 265 patients in the intent-to-treat population as originally randomized are presented in Table 1. The average age was 62.3 years. ACE-inhibitor and angiotensin receptor–blocker therapy was used by 95% and 8% of the patients, respectively. Groups were well matched for most variables. Of the 265 randomized patients, 204 (77%) completed the dose optimization and maintenance phases. The maximal dose level was taken at end point in all patients in the lowest-dose groups, in >90% of those in the 0.9- to 1.2-mg-BID dose groups, and in 79% in the high-dose group.
Norepinephrine

A marked, statistically significant dose-related decrease in plasma norepinephrine levels was observed from baseline to predose levels at end point ($P=0.0005$) and 4 hours after dose at week 19 ($P=0.0005$ (see Figure or Table 2), where end point is the last measurement at or before week 19. Significant treatment differences between the placebo group and the moxonidine SR groups, except for 0.3-mg-BID group, were observed for the changes in predose plasma norepinephrine from baseline to end point (Table 2). The percent difference from placebo in adjusted means reached $-23.1\%$ to $-46.3\%$ at week 3 and $-10.6\%$ to $-47.1\%$ at week 7 in the 0.3- to 1.5-mg dose groups, respectively. At week 19, plasma norepinephrine decreased further to $-34.1\%$ to $-51.8\%$ in those groups. The moxonidine SR 0.3-mg-BID dose group had 1 patient with a large positive change in norepinephrine level, and this patient may have caused the nonsignificance of the treatment difference in this group at end point.

After drug withdrawal, significant increases in plasma norepinephrine were seen within 1 day. During washout day 3, a significant dose-related rebound was observed in plasma norepinephrine. It was $12.8\%$ (59 pg/mL) in the placebo group and $35.1\%$ (139 pg/mL) in the 0.3-mg group up to $275\%$ (709 pg/mL) in the 1.5-mg-BID dose group.

Blood Pressure and Heart Rate

The adjusted mean change in predose supine systolic blood pressure did not show any significant dose-related decrease from baseline to end point (Table 3). During washout, a nonsignificant trend ($P=0.065$) in favor of an increase in systolic blood pressure was observed. Supine heart rate decreased significantly from baseline to end point in a dose-related manner ($P=0.001$). The decrease was modest, with an adjusted mean reduction of 6.7 bpm in the 1.5-mg-BID dose group. During the washout period, significant increases in heart rate were seen within 1 day. During...
washout day 3, there was a significant dose-related increase in heart rate ($P<0.0005$).

**Left Ventricular Ejection Fraction**

All moxonidine SR treatment groups demonstrated an increase in the adjusted mean LVEF from baseline to end point (Table 4). There was a statistically significant dose-related increase ($P=0.015$). The increase was significant compared with placebo for only the moxonidine SR 1.2-mg-BID group, in which it increased 7% units ($P=0.007$).

**Holter Recording**

There was no dose-dependent trend for change from baseline to washout. During washout, however, there were up to 20% to 30% of individual patients in the higher-dose groups that had a clearly greater increase in ventricular extrasystoles (up to 20% to 30% more) and ventricular couplets relative to those seen in placebo patients.

**Side Effects**

All patients randomized to the target moxonidine SR doses of 0.3 and 0.6 mg BID were able to achieve and maintain to end point the target dose of study drug. In the 0.9-mg- and 1.2-mg-BID dose groups, $\approx 90\%$ of the subjects tolerated the target dose to end point. Only 79% of patients in the 1.5-mg-BID dose group could be maintained on this dose to end point.

Treatment-emergent adverse events with a $\geq 5\%$ incidence in any moxonidine SR treatment group during dose optimization and maintenance were selected for evaluation. In this group of selected adverse events, 55.3% of the patients in the placebo group, compared with 76.7%, 63.6%, 75.5%, 75.0%, and 76.6% of the patients in the moxonidine SR 0.3-, 0.6-, 0.9-, 1.2-, and 1.5-mg-BID dose groups, respectively, had $\geq 1$ or more adverse events. The occurrence of dry mouth, dizziness, and asthenia in the moxonidine SR groups was largely responsible for this difference seen between placebo-treated and moxonidine SR–treated patients.

Although there was no dose-response relationship for the moxonidine SR dose groups, from end point to the end of washout, headache and dizziness were the most common discontinuation-emergent adverse events, ie, events that began or worsened during the dose tapering or washout phases. In patients who underwent dose tapering, the most common adverse event was dyspnea, but more patients in the placebo-treatment group experienced this adverse event than in the moxonidine SR–treatment group.

During the dose-optimization and maintenance phases, serious adverse events were reported in 60 patients. These events included deaths and are presented in Table 5. In relation to moxonidine dose, there was a significant ($P=0.038$) trend for an increase in the percentage of patients who had $\geq 1$ serious adverse event. A total of 43 randomized patients withdrew from the study because of adverse events or death (Table 5). In the placebo group, 3 patients (7.9%) withdrew, compared with 18.4% to 23.4% in the moxonidine SR groups. No relationship with dose was noted.

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**TABLE 2. Dose-Related Change in Supine Predose Plasma Norepinephrine Concentration (pg/ml)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=36)</th>
<th>0.3 (n=42)</th>
<th>0.6 (n=39)</th>
<th>0.9 (n=42)</th>
<th>1.2 (n=40)</th>
<th>1.5 (n=36)</th>
<th>Dose-Trend $P$ (One-Sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>393 (195)</td>
<td>416 (235)</td>
<td>381 (214)</td>
<td>433 (263)</td>
<td>397 (324)</td>
<td>460 (285)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>369</td>
<td>376</td>
<td>327</td>
<td>377</td>
<td>335</td>
<td>394</td>
<td></td>
</tr>
<tr>
<td><strong>End point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>510 (232)</td>
<td>476 (393)</td>
<td>323 (198)</td>
<td>284 (169)</td>
<td>286 (156)</td>
<td>260 (157)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>483</td>
<td>389</td>
<td>263</td>
<td>264</td>
<td>233</td>
<td>249</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline to end point</strong>§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adj Mean Change</td>
<td>105</td>
<td>61</td>
<td>$-77$</td>
<td>$-138$</td>
<td>$-121$</td>
<td>$-172$</td>
<td>$&lt;0.0005$</td>
</tr>
<tr>
<td>$P$</td>
<td>0.366</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline to 4 hours</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Postdose at week 19†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>28</td>
<td>31</td>
<td>31</td>
<td>28</td>
<td>28</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Adj Mean Change</td>
<td>114</td>
<td>68</td>
<td>$-62$</td>
<td>$-93$</td>
<td>$-121$</td>
<td>$-137$</td>
<td>$&lt;0.0005$</td>
</tr>
<tr>
<td>$P$</td>
<td>0.387</td>
<td>0.001</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td></td>
</tr>
<tr>
<td><strong>End point to washout day 3‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>28</td>
<td>29</td>
<td>30</td>
<td>28</td>
<td>26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Adj Mean Change</td>
<td>59</td>
<td>139</td>
<td>417</td>
<td>348</td>
<td>592</td>
<td>709</td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td>0.361</td>
<td>$&lt;0.0005$</td>
<td>0.001</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
<td>$&lt;0.0005$</td>
</tr>
</tbody>
</table>

*Patients with data at baseline and end point.
†Patients with data at end point and 4 hours postdose at week 19.
‡Patients with data at end point and washout day 3.
§$P$ for treatment by baseline interaction $<0.0005$.
||$P$ for treatment by baseline interaction $=0.006$. 

*Patients with data at baseline and end point.
†Patients with data at end point and 4 hours postdose at week 19.
‡Patients with data at end point and washout day 3.
§$P$ for treatment by baseline interaction $<0.0005$.
||$P$ for treatment by baseline interaction $=0.006$. 

A total of 10 patients died during the dose-optimization and maintenance phases: 1, 4, 3, and 2 deaths occurred in the moxonidine SR 0.3-, 0.9-, 1.2-, and 1.5-mg-BID dose groups, respectively. There were no deaths in the placebo or moxonidine SR 0.6-mg-BID dose groups. No relationship with dose was noted. No deaths occurred from end point to the end of the washout phase. There were another 2 deaths from screening to randomization and 2 deaths after study completion.

Discussion
The MOXSE study demonstrated a significant dose-dependent reduction of plasma norepinephrine concentrations by moxonidine SR in patients with chronic heart failure. The decrease was marked and reached 23.1% to 46.3% compared with the placebo group within the first 3 weeks, when patients were still in dose uptitration. The effect on systolic blood pressure was small, and heart rate decreased by an average 6.7 bpm with the top dose. After drug withdrawal, significant increases in plasma norepinephrine and heart rate were seen within 1 day. These effects of moxonidine SR were similar to those recently reported after a dose of moxonidine SR of 0.9 mg BID in a smaller number of subjects with chronic mild-to-moderate heart failure.15

The decrease in plasma norepinephrine noted between moxonidine SR doses of 0.3 and 1.5 mg BID was associated with an increase in LVEF measured in a subset of subjects. The increase in LVEF was from 2 EF units at the lowest moxonidine doses to 7 and 5 LVEF units at the 1.2- and 1.5-mg-BID doses, respectively, which reached statistical significance by the dose-trend test. Thus, lowering adrenergic activity by a centrally acting mechanism appears to produce an effect on left ventricular function that is qualitatively similar to that observed with β-blocking agents.17

Systemic and cardiac sympathetic activity are increased in chronic heart failure. Plasma norepinephrine collected by peripheral blood sampling reflects total sympathetic activation in chronic heart failure, with the contribution of cardiac sympathetic activation underestimated because of dilution by less activated regional sources.1 In patients not treated with ACE inhibitors, plasma norepinephrine concentrations are related to the degree of chronic heart failure,19 and the

### TABLE 3. Dose-Related Change in Predose Supine Systolic Blood Pressure and Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Moxonidine SR, mg BID</th>
<th>Dose-Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Supine systolic blood pressure, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to end point</td>
<td>n 38</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Adj Mean Change</td>
<td>-2.7</td>
<td>-1.3</td>
<td>-2.0</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.668</td>
<td>0.834</td>
<td>0.529</td>
</tr>
<tr>
<td>End point to washout day 3</td>
<td>n 31</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>Adj Mean Change</td>
<td>3.0</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.616</td>
<td>0.599</td>
<td>0.447</td>
</tr>
<tr>
<td><strong>Supine heart rate, bpm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to end point</td>
<td>n 38</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Adj Mean Change</td>
<td>-3.2</td>
<td>-3.9</td>
<td>-6.1</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.060</td>
<td>0.028</td>
<td>0.001</td>
</tr>
<tr>
<td>End point to washout day 3</td>
<td>n 30</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Adj Mean Change</td>
<td>4.6</td>
<td>9.4</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.291</td>
<td>0.012</td>
<td>0.004</td>
</tr>
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</table>

### TABLE 4. Dose-Related Change in Left Ventricular Ejection Fraction (%) from Baseline to End Point: Intent-to-Treat-Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=18)</th>
<th>Moxonidine SR, mg BID</th>
<th>Dose-Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3 (n=26)</td>
<td>0.6 (n=25)</td>
<td>0.9 (n=27)</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>24 (5)</td>
<td>24 (7)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>End point, mean (SD)</td>
<td>24 (6)</td>
<td>26 (13)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Baseline to end point</td>
<td>Adj Mean Change</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.300</td>
<td>0.326</td>
<td>0.361</td>
</tr>
</tbody>
</table>
absolute levels have prognostic implications. Over time, plasma norepinephrine increases as heart failure progresses.

The principal adverse effects associated with moxonidine SR administration were dry mouth, dizziness, and asthenia, which are known to be associated with agonist activation of central imidazoline or α2-adrenergic receptors. During the washout phase, headache and dizziness were reported, which might reflect the rebound increase in sympathetic activation during this period. Although moxonidine SR was well tolerated in doses of 0.3 to 1.5 mg BID, there was a trend toward more subjects withdrawing from the study because of adverse events in all moxonidine arms except for the 0.6-mg-BID group. In addition, although the small numbers preclude statistical assessment, there were more deaths in the 0.9- to 1.5-mg-BID moxonidine SR groups. However, no relationship with dose was noted. The rebound increase in plasma norepinephrine during washout was dose related and varied from +12% in the 0.3-mg group to +275% in the 1.5-mg group. It was accompanied by an increase in heart rate and blood pressure and premature ventricular beats. This rebound should cause some concern even if we did not confirm adverse events in this trial. However, a recently conducted mortality trial with titration from 0.25 mg BID up to, but not to exceed, the maximum dose of 1.5 mg BID of moxonidine SR was prematurely discontinued because of an excess of mortality compared with the placebo. The rebound phenomenon observed here might have relevance to the adverse outcome in the Moxonidine Congestive Heart Failure Trial (MOXCON).

There are many possible explanations for the moxonidine dose–related increase in serious adverse events observed in this study that might also explain the increase in mortality noted in MOXCON. One possible explanation is the marked sympatholytic effect of doses of moxonidine SR ≥0.9 mg BID, which encompasses the target doses used in MOXCON. This antiadrenergic effect would be expected to produce myocardial depression, and because the pharmacological mechanism is a reduction in sympathetic outflow, the β-adrenergic support mechanism could not be accessed while the drug is being administered. This differs from β-blocking agents, which produce a reversible blockade whereby increased norepinephrine release can overcome competitive β-blockade if necessary. Another possible explanation for the adverse events associated with higher doses of moxonidine SR is a sympathetic withdrawal phenomenon related to noncompliance or delayed drug administration. This seems less likely, because no mortality was observed during the withdrawal phase and there was no obvious relationship between adverse events and noncompliance. In addition, another agent with sympatholytic properties, bucindolol, has recently had marked norepinephrine lowering linked to an increased mortality risk.

Thus, it would appear that in subjects with chronic heart failure, production of a powerful antiadrenergic effect by sympatholysis can result in favorable reverse remodeling but may be associated with an increased risk for serious adverse events in subjects hemodynamically dependent on adrenergic drive.

Study limitations are primarily the size of the study, which precludes assessment of any clinical efficacy end points from the marked reduction of plasma norepinephrine.

**Conclusions**

In conclusion, the increased sympathetic activation in chronic heart failure can be reduced by the imidazoline ligand moxonidine, probably by its action on a population of adrenergic/imidazoline-receptive sites within the central nervous system. Furthermore, the decrease in adrenergic activity is associated with some of the favorable effects that have previously been reported with β-receptor blockade. Conversely, the trend toward an increase in serious adverse events in subjects treated with moxonidine may mean that there are fundamental differences between delivering an antiadrenergic treatment via sympatholysis versus β-receptor blockade.

**Appendix**

The following persons participated in the MOXSE trial. **Belgium:** Dia El Allaf, Huy; Michel Vandermotte, Antwerp. **France:** Noël Baille, Metz; Bernard d’Hautefeuille, Beuvry/Bethune; Thomas Drawin, Saint-Die; Gery Hannebicque, Arras; Jean Ernst Poulard, Abbeville; Faiez Zannad, Dommartin les Touil. **Germany:** Harald Darius, Mainz; Veselin Mitrovic, Bad Nauheim; Wolfgang Motz, Karlsruhe. **Netherlands:** Peter Bemink, Groningen; Simon Braat, Maastricht; Herman Michels, Eindhoven; Adriana Schelling, Rotterdam; Ernst van der Wall, Leiden; Dirk Jan van Veldhuisen,
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References


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