α1-Antagonists in the Treatment of Hypertension

Richard H. Grimm Jr.

A number of agents are now available to treat hypertension. One relatively new class of agents is the selective α1-inhibitors, which have distinct advantages over earlier nonselective α-adrenergic receptor-blocking agents. Three α1-inhibitors are reviewed in this article: prazosin, terazosin, and doxazosin. These α1-inhibitors are similar in chemical structure and pharmacological action. α1-Inhibitors lower blood pressure by reducing vascular tone in resistance and capacitance vessels. α1-Inhibitors are similar in effectiveness in blood pressure lowering to other commonly used antihypertensive agents like the thiazide diuretic drugs and β-blockers, which are efficacious as monotherapy in lowering pressure, as initial agents, or in combination with other antihypertensive agents in multidrug therapeutic regimens. α1-Inhibitors are associated with a reasonably low incidence of serious adverse effects and are essentially free of any adverse metabolic effects. α1-Inhibitors have been shown to beneficially effect blood lipids in several studies. The favorable lipid effect makes α1-inhibitors especially appropriate to use in diabetic hypertensive and other patients with elevated serum lipid levels. The beneficial lipid effects may enhance the ability of α1-inhibitors to prevent coronary heart disease, an outcome that has been difficult to demonstrate in thiazide-based trials. (Hypertension 1989;13(suppl I):I-131—I-136)

A great deal of progress has been made during the past 30 years in developing drugs to treat hypertension. Today, the practitioner can select among several different classes of pharmacological agents, all of which are effective in lowering blood pressure and which have manageable side effects. Nonselective α-inhibitors like phenoxybenzamine and phentolamine were first used to treat hypertension in the mid-1950s. However, their usefulness was limited because of poor blood pressure-lowering efficacy and a high rate of unfavorable side effects, primarily marked tachycardia and a rapid development of loss of blood pressure efficacy. Therapeutic interest in α-inhibition has been renewed by the development of drugs that possess adrenoreceptor selectively. This new generation of α-inhibitors has many advantages over the original nonselective agents.

In 1976, the first selective α1-inhibitor, prazosin, was introduced. Prazosin was highly preferable to previous α-inhibitors because it appeared to maintain local receptor-operator control mechanisms. From the Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, Minnesota.

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Tachycardia and tolerance have not been problems with prazosin, an agent that has been used extensively for more than 10 years to treat hypertension. The selective α1-inhibitors reviewed in this article are all quinazoline derivatives, which include prazosin, terazosin, and doxazosin. The chemical structures of these compounds are similar (Figure 1); terazosin differs from prazosin only in that the furan ring of the terazosin molecule is saturated. This structural difference accounts for terazosin’s longer half-life and allows this drug to be used once daily. The structure of doxazosin also allows for a longer duration of action and once-daily dosing. The pharmacology of the selective α1-agents has recently been reviewed by Kyncl and Davey.

Selective α1-Inhibitors—Mechanism of Action

Selective α1-inhibitors are all effective agents for lowering blood pressure by reducing peripheral vascular tone in resistance and capacitance vessels. This group of agents is highly selective for the postsynaptic α1-receptors. This unique action probably allows the selective α1-inhibitors to preserve feedback control on norepinephrine release, which may be responsible for preventing the undesired side effects of tachycardia and tolerance.

Selective α1-Inhibitors and Blood Pressure Control

The selective α1-inhibitors, prazosin, terazosin, and doxazosin, have all been found to significantly
lower blood pressure in patients with uncomplicated hypertension. Prazosin has been demonstrated to be an effective antihypertensive agent in a number of studies. A recent report compared blood pressure lowering with terazosin to a placebo in a series of controlled trials (Table I). These trials were fixed-dose and titration studies with daily doses of terazosin ranging from 1 mg to 40 mg. Study participants were men and women ranging from 21 to 72 years old. Although these studies were not primarily designed to evaluate maximum blood pressure reduction, they showed that terazosin significantly lowered systolic and diastolic blood pressure by 8–12 mm Hg, an effect significantly different from placebo. Additional analyses from these studies showed the diastolic blood pressure response to the α₁-inhibitor to be excellent. The response was very good or good (diastolic blood pressure <90 mm Hg at the final visit, a decrease of at least 10 mm Hg from baseline, or a decrease of 7–10 mm Hg from baseline but >90 mm Hg at the final visit) in 48% of those receiving terazosin compared with 33% taking placebo (p < 0.05). Another study found that doxazosin and prazosin also lower blood pressure substantially compared with placebo, with observed changes in systolic and diastolic blood pressure for the α-blocker similar to those reported for terazosin.

The hypotensive effect of selective α₁-inhibitors has also been compared directly with that of the thiazide diuretic agents. Stamler et al. reported preliminary data on 62 hypertensive men and women in a randomized controlled trial comparing prazosin and hydrochlorothiazide. Participants were observed for a 3-month follow-up period. Both agents lowered diastolic blood pressure by a similar amount, averaging 10–11% for prazosin and 8–9% for hydrochlorothiazide. Doxazosin has also been compared with hydrochlorothiazide in double-blind controlled studies. In dosages of 1–16 mg doxazosin/day and 25–100 mg/hydrochlorothiazide/day, the two drugs showed similar results by significantly lowering standing and supine systolic and diastolic pressures. Both agents were clearly superior to placebo.

The α₁-inhibitors prazosin and doxazosin have been compared with a number of β-adrenergic receptor-blocking agents. In several studies, systolic and diastolic blood pressure lowering is similar (8–12%) when selective α₁-inhibitors are compared with various β-blockers.

Blood pressure lowering with selective α₁-inhibitors has also been studied by combining α-blockers with a variety of other classes of antihypertensive medications including diuretic agents and several β-blockers. These studies have found additional efficacy by adding α-inhibitors to these other agents.

**Metabolic Effects of α₁-Inhibitors**

One major advantage of α₁-inhibitors is that they are essentially free of significant adverse metabolic effects. In controlled studies, the use of these agents has not been associated with significant adverse metabolic effects. In fact, several studies have observed that α₁-inhibitors favorably benefit blood lipid levels. Table 2 summarizes lipid results from studies with the α₁-inhibitors prazosin, terazosin, and doxazosin. Generally, this group of agents modestly lowers blood total cholesterol, low density lipoprotein cholesterol,
TABLE 1. Blood Pressure Response* to Terazosin in Five Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Mean baseline supine</th>
<th>Mean baseline standing</th>
<th>Mean change in supine</th>
<th>Mean change in standing</th>
<th>Percent change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Terazosin</td>
<td>Placebo</td>
<td>SBP</td>
<td>DBP</td>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>M79-056</td>
<td>11</td>
<td>10</td>
<td>102±1.6</td>
<td>102±1.6</td>
<td>143±3.8</td>
<td>103±1.7</td>
</tr>
<tr>
<td>M80-033</td>
<td>17</td>
<td>14</td>
<td>101±2.0</td>
<td>101±2.0</td>
<td>155±3.6</td>
<td>107±2.2</td>
</tr>
<tr>
<td>M81-059</td>
<td>48</td>
<td>31</td>
<td>100±1.5</td>
<td>100±1.5</td>
<td>156±3.8</td>
<td>108±2.2</td>
</tr>
<tr>
<td>M81-060</td>
<td>54</td>
<td>39</td>
<td>101±0.6</td>
<td>101±0.6</td>
<td>149±2.0</td>
<td>100±0.9</td>
</tr>
<tr>
<td>M81-061</td>
<td>39</td>
<td>26</td>
<td>101±0.7</td>
<td>101±0.7</td>
<td>154±2.5</td>
<td>101±1.1</td>
</tr>
</tbody>
</table>

*All blood pressure values are in mm Hg.

†Significant difference between treatment groups (p<0.05).

SBP: systolic blood pressure; DBP, diastolic blood pressure; T, terazosin; and P, placebo.


Side Effects of a,-Inhibitors

Although no drug is totally free of side effects, a,-inhibitors as a group are associated with relatively low incidence and severity of side effects. Overall, the most common adverse experiences associated with a,-inhibitors are dizziness and asthenia. Frank syncope is similar to that reported with other classes of antihypertensive agents. The overall incidence of side effects is not greater than that of placebo. The most common adverse experiences associated with a,-inhibitors are dizziness and asthenia, similar to other commonly used classes of agents. A similar incidence of serious side effects and withdrawal from a,-inhibitors because of adverse experiences is demonstrated in the patients treated with a,-inhibitors as a group.

Serious side effects that have been reported include vertigo, tiredness, or fatigue, and asthenia. The incidence of somnolence occurs at a rate of 5–10% and tachycardia and increased heart rate have been reported. The most common adverse effects associated with a,-inhibitors are dizziness and asthenia. The incidence of dizziness has been shown to be higher than that associated with other classes of antihypertensive agents. The overall incidence of side effects is not greater than that of placebo. The most common adverse experiences associated with a,-inhibitors are dizziness and asthenia, similar to other commonly used classes of agents. A similar incidence of serious side effects and withdrawal from a,-inhibitors because of adverse experiences is demonstrated in the patients treated with a,-inhibitors as a group. The overall incidence of side effects is not greater than that of placebo. The most common adverse experiences associated with a,-inhibitors are dizziness and asthenia, similar to other commonly used classes of agents. A similar incidence of serious side effects and withdrawal from a,-inhibitors because of adverse experiences is demonstrated in the patients treated with a,-inhibitors as a group.

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Table 2. Effects of \(\alpha_1\)-Antagonists on Lipids and Lipoproteins: Within-Group Changes From Baseline by Study

<table>
<thead>
<tr>
<th>Agent and first author</th>
<th>Year</th>
<th>Duration of study (weeks)</th>
<th>Serum lipid measurements*</th>
<th>LDL cholesterol*</th>
<th>HDL cholesterol*</th>
<th>Triglycerides*</th>
<th>Cholesterol/ HDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prazosin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kirkendall et al (^{21})</td>
<td>1978</td>
<td>13</td>
<td>8</td>
<td>-5.3(\uparrow)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Leren et al (^{22})</td>
<td>1980</td>
<td>23</td>
<td>8</td>
<td>-9.0</td>
<td>. . .</td>
<td>-4.0(\uparrow)</td>
<td>-16.5(\uparrow)</td>
</tr>
<tr>
<td>Leichter and Baumgardner (^{23})</td>
<td>1981</td>
<td>7</td>
<td>. . .</td>
<td>-4.3</td>
<td>. . .</td>
<td>+6.0</td>
<td>+4.0</td>
</tr>
<tr>
<td>Velasco et al (^{24})</td>
<td>1982</td>
<td>19</td>
<td>12</td>
<td>+7.5</td>
<td>-2.2</td>
<td>+19.6(\uparrow)</td>
<td>-27.6(\uparrow)</td>
</tr>
<tr>
<td>Kokubu et al (^{25})</td>
<td>1982</td>
<td>14</td>
<td>12</td>
<td>-0.7</td>
<td>. . .</td>
<td>+12.5(\uparrow)</td>
<td>0.9</td>
</tr>
<tr>
<td>Havard et al (^{26})</td>
<td>1982</td>
<td>17</td>
<td>10</td>
<td>0</td>
<td>. . .</td>
<td>+10.5</td>
<td>-16.2</td>
</tr>
<tr>
<td>Litthell et al (^{27})</td>
<td>1982</td>
<td>9</td>
<td>52</td>
<td>-3.2</td>
<td>-6.5</td>
<td>0</td>
<td>-0.7</td>
</tr>
<tr>
<td>Goto (^{28})</td>
<td>1984</td>
<td>24</td>
<td>12</td>
<td>-1.1</td>
<td>+1.0</td>
<td>+4.0</td>
<td>-21.0</td>
</tr>
<tr>
<td>Lowenstein and Neusy (^{29})</td>
<td>1984</td>
<td>29</td>
<td>8</td>
<td>-7.3</td>
<td>-9.4</td>
<td>+6.0</td>
<td>-20.0</td>
</tr>
<tr>
<td>Mauersberger (^{30})</td>
<td>1984</td>
<td>15</td>
<td>8</td>
<td>-2.3</td>
<td>-15%</td>
<td>+10.8(\uparrow)</td>
<td>-3.2</td>
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<tr>
<td>Rouff (^{31})</td>
<td>1984</td>
<td>24</td>
<td>13</td>
<td>-7.9(\uparrow)</td>
<td>-13.4(\uparrow)</td>
<td>+13.1(\uparrow)</td>
<td>-9.9(\uparrow)</td>
</tr>
<tr>
<td>Tskabatake et al (^{32})</td>
<td>1984</td>
<td>15</td>
<td>52</td>
<td>+2.0</td>
<td>. . .</td>
<td>+17.0(\uparrow)</td>
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<td>32 variable</td>
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<td>-5</td>
<td>+6.1</td>
<td>-12.5</td>
<td>-9.5</td>
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<td>128</td>
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<td>+1.6</td>
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<tr>
<td>Deger (^{33})</td>
<td>1986</td>
<td>38</td>
<td>variable</td>
<td>-3.1</td>
<td>-5.6</td>
<td>+4.2</td>
<td>-9.5</td>
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<td><strong>Doxazosin</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Cox et al (^{34})</td>
<td>1986</td>
<td>142</td>
<td>9-24</td>
<td>-1.2</td>
<td>. . .</td>
<td>+7.6</td>
<td>-9.0</td>
</tr>
<tr>
<td>Lehtonen et al (^{35})</td>
<td>1986</td>
<td>21</td>
<td>20</td>
<td>-8.9(\uparrow)</td>
<td>-16.9(\uparrow)</td>
<td>+8.0(\uparrow)</td>
<td>-1.1</td>
</tr>
<tr>
<td>Torvik and Madsbu (^{12})</td>
<td>1986</td>
<td>46</td>
<td>12</td>
<td>-3.9</td>
<td>-5.5</td>
<td>+6.3</td>
<td>-12.6(\uparrow)</td>
</tr>
<tr>
<td>Frick et al (^{36})</td>
<td>1986</td>
<td>39</td>
<td>20</td>
<td>-1.7</td>
<td>. . .</td>
<td>+3.9(\uparrow)</td>
<td>-5.0(\uparrow)</td>
</tr>
<tr>
<td>Pool (^{37})</td>
<td>1987</td>
<td>43</td>
<td>10-24</td>
<td>+1.3</td>
<td>. . .</td>
<td>+0.8</td>
<td>-6.0(\uparrow)</td>
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<tr>
<td>Nash et al (^{38})</td>
<td>1987</td>
<td>38</td>
<td>10</td>
<td>-2.9(\uparrow)</td>
<td>. . .</td>
<td>+2.1(\uparrow)</td>
<td>-11.1(\uparrow)</td>
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<tr>
<td>Trost et al (^{38})</td>
<td>1987</td>
<td>19</td>
<td>24</td>
<td>-6.1(\uparrow)</td>
<td>-8.5</td>
<td>+13.0(\uparrow)</td>
<td>-17.4(\uparrow)</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein and HDL, high density lipoprotein. *Values are in mg/dl.

\(*\), Significant change from baseline; \(\ast\), significant change compared with placebo; \(\ast\), significant change compared with thiazide diuretic drug; \(\ddagger\), significant change compared with \(\beta\)-blocker; and \(\ast\), significant change compared with other antihypertensive agent.

\(\uparrow p<0.05\), \(\uparrow p<0.01\), \(\uparrow p<0.001\).

...in studies of terazosin and doxazosin. For all studies, approximately one half of those patients treated with \(\alpha_1\)-inhibitors report at least one adverse effect, which is usually mild to moderate in severity. Frequently, the placebo-treated patients have a similar number of complaints. It is noteworthy that impotence, a common side effect observed with many antihypertensive agents, occurs infrequently with \(\alpha_1\)-inhibitors and is usually not different compared with placebo. \(^{20}\) Treatment with \(\alpha_1\)-inhibitors often results in some weight gain, usually 2-3 pounds, and peripheral edema is occasionally observed. Tachycardia and tolerance, which were common side effects with the earlier...
nonselective \(\alpha\)-inhibitors, are not notable problems with the newer selective \(\alpha\)-inhibitors when used in the treatment of hypertension.

**Discussion**

A number of selective \(\alpha\)-inhibitors have been studied to determine their usefulness as antihypertensive agents. Unlike the early nonselective \(\alpha\)-agents, the newer \(\alpha\)-inhibitors are well tolerated and largely free of important adverse effects like tachycardia, diarrhea, and tolerance.

Selective \(\alpha\)-inhibitors have been shown to be more effective than placebo in blood pressure lowering, with an efficacy similar to that of other commonly used antihypertensive agents like the thiazide diuretic drugs and \(\beta\)-blockers. When \(\alpha\)-inhibitors are added to preexisting multiple-drug regimens, selective \(\alpha\)-blockers also have been shown to provide additional efficacy in lowering blood pressure. \(\alpha\)-Blockers are versatile and can be used alone as initial therapy or in combination with other agents in multidrug regimens. \(\alpha\)-Inhibitors as monotherapy will adequately control blood pressure in approximately one half the patients treated for "mild" diuretic hypertension (diastolic blood pressure 90–104 mm Hg). Selective \(\alpha\)-inhibition lowers blood pressure by reducing the peripheral vascular tone in resistance and capacitance vessels.

Selective \(\alpha\)-inhibitors are virtually free of adverse metabolic effects and offer at least theoretical advantages for treating hypertension in patients who also have diabetes, asthma, and peripheral vascular disease. Thus, these agents should be considered as initial antihypertensive agents for these patients. Because selective \(\alpha\)-inhibitors are associated with slightly positive or neutral effects on blood lipoproteins, these drugs should also be considered, along with other lipid-neutral agents, as antihypertensive agents of choice for patients whose blood lipid levels require medical attention. New guidelines considerably broaden the number of patients who require treatment of their blood lipid levels.45

Like all drugs, selective \(\alpha\)-inhibitors are associated with adverse effects. Approximately one half the patients taking \(\alpha\)-blockers on a long-term basis will experience at least one side effect. These side effects are usually mild to moderate in severity. Dizziness, vertigo, asthenia, and fatigue are the most common side effects. The first-dose phenomenon, however, is rare (<1%) when \(\alpha\)-inhibitors are given in small, carefully titrated, initial doses at bedtime.

Further investigation of selective \(\alpha\)-inhibitors and other antihypertensive agents is needed to determine if the lack or presence of metabolic effects, like those on lipid and lipoprotein concentrations, is significant in preventing cardiovascular disease independent of the blood pressure-lowering effects, which are generally similar for most antihypertensive agents. The Treatment of Mild Hypertension Study is one that is currently addressing this important question in a long-term trial.46

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KEY WORDS: α-inhibitors • antihypertensive agents • α-blockers
alpha 1-antagonists in the treatment of hypertension.
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Hypertension. 1989;13:I131
doi: 10.1161/01.HYP.13.5_Suppl.I131

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