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## Isradipine in the treatment of hypertension: a clinical profile

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■ Isradipine (DynaCirc, PK 200-110) is a new calcium channel blocker of the dihydropyridine class. In controlled, double-blind, clinical trials isradipine is an effective first-line monotherapeutic agent in the treatment of hypertension, regardless of patient age or race. Isradipine is safe and well tolerated, with few adverse effects reported, and does not cause significant changes in cardiac conduction or the force of cardiac contraction. In addition, it does not adversely affect the lipid profile, carbohydrate tolerance, or renal function. Long-term experience with isradipine indicates that the antihypertensive efficacy is maintained without problems of tachycardia or tachyphylaxis.

□ INDEX TERMS: HYPERTENSION; ISRADIPINE □ CLEVE CLIN J MED 1990; 57:677-684

**A**N IDEAL antihypertensive agent would effectively lower blood pressure by correcting the hemodynamic variable that is out of alignment, while being well tolerated and safe. Characteristics would include reduction of total peripheral resistance, maintenance of systemic and regional blood flow, preservation of cardiac function, and prevention of fluid and salt retention.<sup>1</sup> Patient compliance is enhanced if the agent can be administered as monotherapy without frequent dosing.<sup>2</sup>

Because calcium channel blockers have the potential to meet many of these requirements, they have become

attractive antihypertensive agents. Isradipine (DynaCirc, PK 200-110), a new dihydropyridine-derivative calcium channel blocker, is emerging as an especially promising agent. It now awaits approval by the Food and Drug Administration and is expected to be available early in 1991.

### HETEROGENEITY OF CALCIUM CHANNEL BLOCKERS

Calcium channel blockers comprise a heterogeneous group of compounds that vary in chemical structure and in pharmacologic profile. Currently, three types of calcium channel blockers are available: the dihydropyridines nifedipine and nicardipine, the papaverine derivative verapamil, and the benzothiazepine diltiazem. While all are peripheral vasodilators, they differ in their hemodynamic and pharmacologic profiles, efficacy, and side effects.<sup>3</sup>

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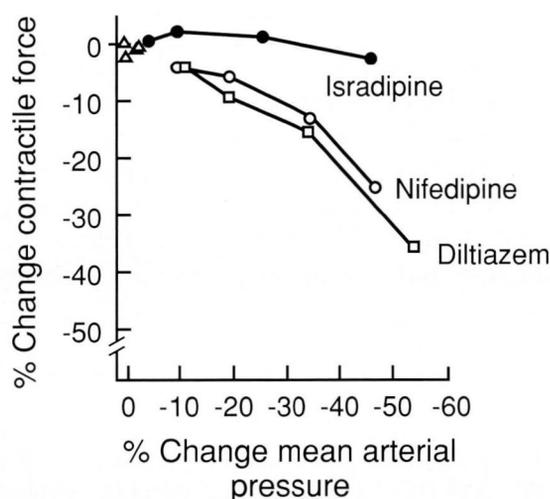
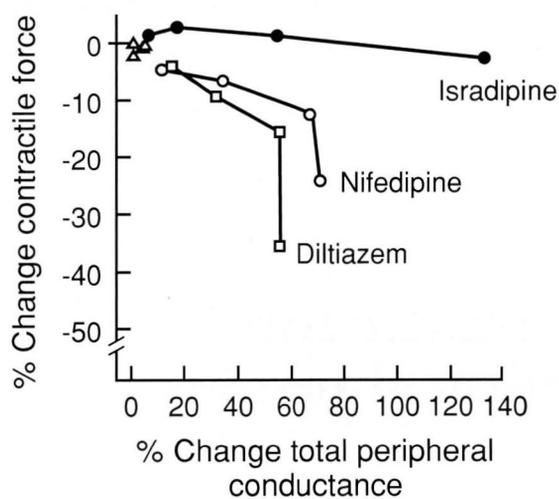


FIGURE 1. Changes in myocardial contractility plotted as a function of increases in total peripheral conductance, top, or as a function of decreases in blood pressure, bottom. The effects are expressed as percent of change from baseline values.  $\Delta$  (near the y-axis), changes occurring in the control group. (Adapted from Hof<sup>9</sup> with permission of the author and publisher.)

All calcium channel blockers share the common mechanism of blockade of the voltage-dependent calcium channel as well as certain characteristic effects. However, they can be differentiated by their site selectivities, including selectivity for the vasculature *v* the myocardium, for certain vascular beds within the vasculature, and for different tissues in the heart. It is generally agreed that calcium channel blockers derived

from the dihydropyridine class are more vasoselective and less cardiodepressant than nondihydropyridine calcium channel blockers such as verapamil or diltiazem. In addition, within the dihydropyridine group, the newer agents seem to have greater selectivities than, for example, nifedipine, the prototype dihydropyridine.

#### EXPERIMENTAL STUDIES

In animals, isradipine is a powerful vasodilator, showing considerable selectivity for vascular smooth muscle over myocardial tissue.<sup>4,5</sup> It preferentially dilates coronary, cerebral, and skeletal muscle vasculature,<sup>6</sup> and has a long duration of action. Isradipine also has cardioprotective effects after ischemia, due to preservation of the blood flow to the inner layer of the left ventricle after the ischemic period.<sup>7</sup>

While the main actions of calcium channel blockers are vasodilation and myocardial depression, the degree of cardiodepressant action compared to vasodilator action varies from one agent to another. It is particularly important to differentiate conduction from contraction effects because of interest in identifying an agent that has the clinical advantages of verapamil or diltiazem combined with the low cardiodepressant properties of the dihydropyridines.<sup>8</sup>

#### In vitro studies

In *in vitro* studies, isradipine differed from nifedipine, verapamil, and diltiazem, as well as even the structurally similar darodipine.<sup>4</sup> While having one of the highest selectivities for coronary blood flow *v* cardiac activities, isradipine was unique in that it inhibited the sinoatrial (SA) node with little effect on atrioventricular (AV) conduction. In addition, isradipine caused little suppression of cardiac muscle contraction. The cardiovascular profiles determined from such experiments for calcium channel blockers in clinical use have been shown to correlate with the profiles observed in patients.<sup>4</sup>

#### In vivo studies

In open-chest dogs, isradipine markedly increased coronary flow, lowered blood pressure, and increased cardiac output, but tended to lower heart rate and increase myocardial contractility.<sup>6</sup> Despite the lack of cardiodepression, myocardial oxygen consumption was markedly lowered.

The cardiodepressant and vasodilator effects of isradipine, nifedipine, and diltiazem were compared in rabbits with compensatory baroreceptor-mediated

reflexes eliminated.<sup>9</sup> The effects of all three agents on blood pressure were similar, but isradipine produced the greatest peripheral vasodilation and increase in cardiac output. Isradipine did not decrease myocardial contractile force, even in doses that decreased blood pressure by 43%, and it increased peripheral vasodilation by 134%. The efficacy of nifedipine and diltiazem was limited by the cardiodepression that they caused. The changes in myocardial contractility as a function of increases in total peripheral resistance and decreases in blood pressure for isradipine, nifedipine, and diltiazem are shown in *Figure 1*. Isradipine caused a minimal decrease in heart rate, whereas nifedipine caused none.<sup>9</sup>

Isradipine has also been shown to have natriuretic and diuretic effects in conscious, normotensive rats.<sup>10</sup> These effects occurred at doses that were associated with antihypertensive effects.

#### CLINICAL PHARMACOLOGY

Isradipine binds to calcium channels with a very high affinity and excellent specificity.<sup>10</sup> Pharmacokinetic studies indicate that isradipine is rapidly and completely absorbed following oral administration.<sup>11</sup> Food has no appreciable effect on the rate and extent of absorption.<sup>12</sup>

Low bioavailability (19%) results from extensive first-pass metabolism.<sup>12</sup> Isradipine is completely metabolized before excretion, and no unchanged drug is detected in the urine. The metabolites are pharmacologically inactive.<sup>12</sup> The elimination of isradipine is biphasic with a terminal half-life of 8.4 hours. Isradipine had a long half life in several experimental models, and in spontaneously hypertensive rats, blood pressure was still reduced 48 hours after oral administration.<sup>11</sup> In humans, dose-related reductions in supine and standing blood pressures are achieved within 2 to 3 hours following single oral doses of 2.5 mg, 5 mg, 10 mg, and 20 mg, with a duration of action of 24 hours following administration of the highest dose.

In pharmacokinetic studies, there appeared to be a small increase in bioavailability in the elderly, perhaps due to reduced hepatic function.<sup>12</sup> Chellingsworth and associates reported that, overall, the disposition of isradipine did not differ between young and elderly patients.<sup>13</sup> Liver-impaired and renal-impaired subjects had increased plasma levels of isradipine, though the increase was less than has been reported for nitrendipine. The increased drug levels in renal impairment, as well as decreased levels in patients on hemodialysis, are similar to those found with nifedipine.<sup>12</sup>

In general, plasma-level differences between populations studied (young and elderly normal subjects, renal- and liver-impaired patients, and hypertensive patients) were negligible, suggesting that specific dosage adjustment recommendations other than individualized dose titration to accommodate interindividual variability are unnecessary.<sup>12,14</sup>

The coadministration of isradipine and hydrochlorothiazide (HCTZ) resulted in no effect on the bioavailability of either drug.<sup>12</sup> The concomitant administration of isradipine and digoxin did not affect renal, nonrenal, or total body clearance of digoxin,<sup>15</sup> which is not the case with other calcium blockers. Also, isradipine can be safely coadministered with nitroglycerin.

#### EFFICACY IN HYPERTENSION

In an initial, double-blind, placebo-controlled clinical study, Nelson and colleagues found that isradipine monotherapy at a total daily dose of 10 mg significantly decreased blood pressure compared with placebo.<sup>16</sup>

A total of 571 hypertensive patients were entered into five double-blind, controlled, multicenter clinical trials investigating isradipine monotherapy in doses of 2.5 mg to 10 mg administered twice a day.<sup>11,17-22</sup> Each study began with a 3-week placebo washout period, followed by a treatment period of 4 to 10 weeks.

Isradipine treatment resulted in significantly greater reductions from baseline blood pressure compared to placebo (-16.2 mmHg diastolic *v* -59 mmHg) and active controls (-13.0 mmHg for HCTZ, 25 to 50 mg bid; -9.8 mmHg for propranolol, 60 to 240 mg bid; and -13.0 mmHg for prazosin, 2 to 8 mg bid).<sup>17</sup> Eighty-one percent of patients on isradipine had reductions in diastolic blood pressure of at least 10 mmHg, versus 69% on prazosin, 62% on HCTZ, 39% on propranolol, and 32% on placebo.<sup>17</sup> Isradipine resulted in normalization of supine diastolic blood pressure (reduction to 90 mmHg or less) in 66% of patients versus 76% on HCTZ, 61% on prazosin, 42% on propranolol, and 13% on placebo.

Reductions in systolic blood pressure were statistically significant for isradipine (-16.7 mmHg) *v* prazosin (-8.1 mmHg), as well as for isradipine (-19 mmHg) *v* placebo (-4 mmHg).<sup>17</sup>

Patients in these short-term studies were given the option of continuing isradipine treatment for up to 12 months. The antihypertensive efficacy of isradipine was maintained for patients on long-term treatment, with no evidence of tachyphylaxis.<sup>11</sup>

Carr and Prisant studied the efficacy of isradipine

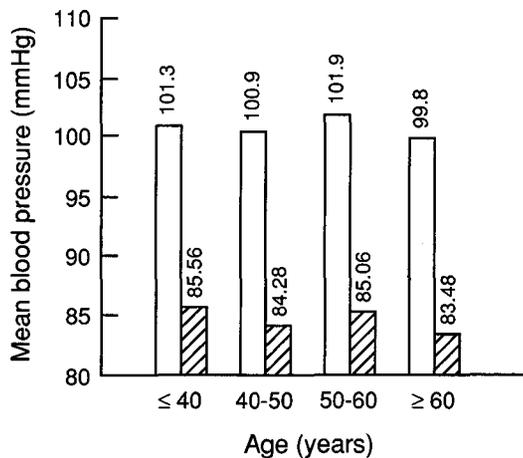


FIGURE 2. Relationship between age and effect on sitting diastolic blood pressure with isradipine treatment. Open bars, baseline levels; shaded bars, endpoint levels. (Adapted from Kirkendall<sup>17</sup> with permission of the author and publisher.)

treatment for 5 weeks (after a 3-week placebo washout period) compared to placebo in black hypertensive patients.<sup>23</sup> An average daily dose of 13.3 mg of isradipine significantly reduced diastolic blood pressure to less than 90 mmHg in 64% of these patients.

Vermeulen and co-investigators compared the effects of isradipine twice a day with diltiazem three times a day for 10 weeks in 95 patients with sitting diastolic blood pressures >100 mmHg.<sup>3</sup> The average isradipine dosage was 13.7 mg per day, and the average diltiazem dosage was 293 mg per day. Isradipine was more effective than diltiazem in lowering systolic blood pressure (−26 mmHg *v* −15 mmHg) and as effective in lowering diastolic blood pressure (−17 mmHg *v* −15 mmHg). Treatment was discontinued due to poor efficacy in five patients receiving diltiazem, but in no patients receiving isradipine.

Rauramaa and associates investigated the use of isradipine or nifedipine for 10 to 13 weeks in 40 hypertensive patients.<sup>24</sup> Isradipine reduced both systolic and diastolic blood pressures by 16 mmHg, and nifedipine reduced both systolic and diastolic blood pressures by 14 mmHg, though the differences between treatment groups were not statistically significant.

In controlled, double-blind clinical trials, isradipine has also been shown to be an effective antihypertensive agent when added to therapy with a thiazide-type diuretic<sup>11</sup> or a beta blocker.<sup>25,26</sup>

These investigations have shown isradipine to be an

effective first-line agent in the treatment of hypertension, with efficacy equivalent to or greater than other first-line agents. It exerts its effect without excessive blood pressure reductions.

### Efficacy across age and race

Different classes of antihypertensive drugs may have varying effectiveness depending on the patient group. For example, older people do not respond as well to beta-blockers and angiotensin-converting enzyme (ACE) inhibitors as do younger people.<sup>27</sup> There is also some evidence that calcium channel blockers as a class may be more effective in older or black hypertensive patients than in younger or white hypertensive patients.<sup>17</sup> Conflicting results have, however, been reported. Nitrendipine, for example, has been shown to be less effective in the elderly than in younger patients.<sup>28</sup> Isradipine has been shown to be an effective first-line agent in the treatment of hypertension, regardless of the age or race of the patient.

**Age.** While patients over 60 years of age had the greatest decreases in diastolic blood pressure in the multicenter clinical studies, isradipine was effective in younger patients (less than 40 years of age) as well (Figure 2). In the older group, isradipine was more effective than propranolol or prazosin in lowering diastolic blood pressure and was equivalent to HCTZ.<sup>17</sup> Pharmacokinetic studies of isradipine in different population groups, including the elderly, suggest that group-specific dosing-adjustment guidelines are not necessary because there were relatively small differences in plasma levels between the groups studied.<sup>12</sup>

**Race.** Isradipine lowered blood pressure to the same degree in both white and black patients. In black patients, isradipine was slightly more effective than propranolol or prazosin and equivalent to HCTZ in lowering blood pressure (Figure 3).<sup>17</sup> While it has been suggested that reductions in blood pressure in response to calcium blockers are greatest in patients with low renin levels, Swartz found no correlation between plasma renin levels and blood pressure reductions caused by isradipine.<sup>21</sup>

### Dosage recommendations

Analysis of the blood pressure response by isradipine dose in the multicenter clinical trials showed that, at each of the four dosage levels, at least 79% of patients had a mean decrease of supine diastolic blood pressure of at least 10 mmHg.<sup>17</sup> Of those patients receiving a dose of 2.5 mg bid, diastolic blood pressure was reduced by at least 10 mmHg in 79% and was normalized (reduced to

90 mmHg or less) in 64%, thus supporting the use of isradipine at lower doses.<sup>17</sup> Most patients responded to isradipine dosages ranging from 5 mg to 15 mg per day, and, in general, there was no additional antihypertensive benefit at dosages greater than 10 mg per day (Figure 4).<sup>11</sup>

It is now generally agreed that up to 3 or 4 weeks is required for the maximal response to isradipine administration to be seen.<sup>29-31</sup> In light of this, the upward titration of doses used in the early clinical trials was probably forced too quickly for the effect of each individual dosage regimen to be evident. Therefore, in many of these studies, the full efficacy of lower dosages may not have been realized. Currently, clinical practice calls for initiating isradipine therapy at a dosage of 5 mg daily (2.5 mg bid), followed by upward titration of the dose over a period of weeks until the optimal clinical response is achieved.<sup>12</sup>

#### ADVERSE EFFECTS

#### Tolerability

In general, isradipine has been shown to be well tolerated. In clinical studies,<sup>17</sup> few adverse reactions were reported, and they were generally dose-related and the result of vasodilation. Side effects can be minimized by starting treatment at low doses and then gradually titrating the dose upward, as opposed to starting with high doses. Overall, there was little difference in the incidence of adverse effects in patients who received isradipine compared with those who received placebo in these trials.<sup>11</sup> As shown in Figure 5, the percentage reporting adverse reactions after the fourth week of treatment among patients who received 10 mg of isradipine daily or less was the same as reported by the placebo-treated patients.<sup>17,30</sup>

The most frequently reported adverse reactions to isradipine in clinical trials were headache, edema, and flushing. When headache occurred, it usually appeared early in treatment and was reduced substantially with continued treatment.<sup>11</sup> Because edema was not associated with weight gain, it is thought that the edema is caused by a microvascular mechanism and is not the

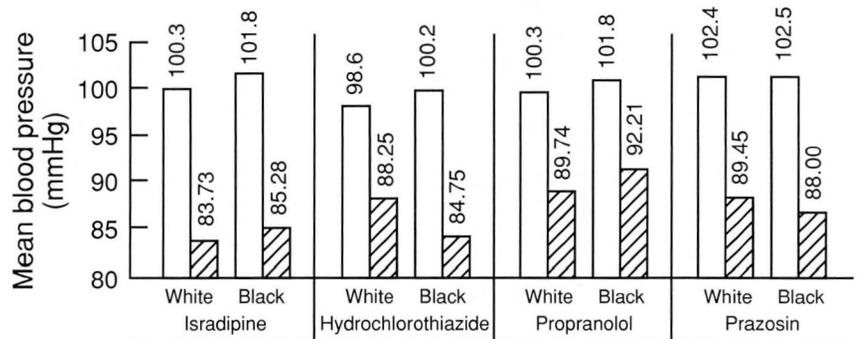


FIGURE 3. Relationship between race and effect on sitting diastolic blood pressure: isradipine *v* active controls. Open bars, baseline levels; shaded bars, endpoint levels. (Adapted from Kirkendall<sup>17</sup> with permission of the author and publisher.)

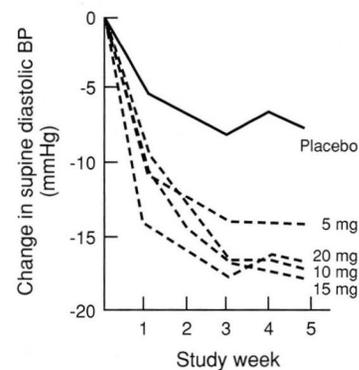


FIGURE 4. Isradipine *v* placebo study: supine diastolic blood pressure change from baseline for 187 valid patients. (Adapted from Kirkendall<sup>17</sup> with permission of the author and publisher.)

result of fluid retention caused by heart failure<sup>3</sup> or sodium retention.<sup>19</sup> Vermeulen reported that when edema was present during isradipine therapy, it was mild.<sup>3</sup> There was no evidence that isradipine produced rebound hypertension, orthostatic hypotension, or impotence.<sup>11</sup>

#### Safety

In general, isradipine appears to be a remarkably safe drug. Areas of particular interest are reviewed below.

**Reflex tachycardia.** Isradipine has been effective in reducing blood pressure without causing reflex tachycardia. In clinical trials, increases in pulse rate of 3 to 6 beats per minute were seen with isradipine therapy.<sup>17</sup> These increases were not deemed clinically significant. In their study comparing isradipine and diltiazem, Ver-

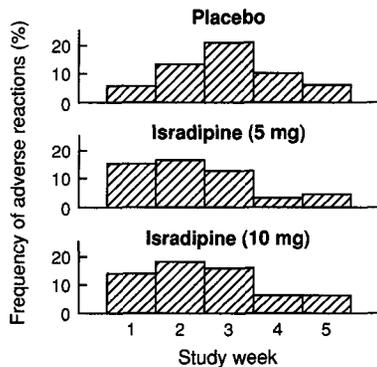


FIGURE 5. Percent frequency of any adverse reactions reported: isradipine v placebo. (Adapted from Kirkendall<sup>17</sup> with permission of the author and publisher.)

meulen and co-workers reported that there was a small, transient increase in heart rate among patients who received isradipine, while there was a significant decrease among those receiving diltiazem.<sup>3</sup> As the study continued, despite increasing dosages of isradipine, mean increases in pulse rates declined. Isradipine's lack of association with reflex tachycardia makes it an attractive alternative for patients who experience palpitations when receiving nifedipine, which has a tendency to cause reflex tachycardia.<sup>13</sup>

**Laboratory abnormalities.** Many antihypertensive agents, such as diuretics and beta blockers, frequently cause alterations in serum chemical values.<sup>27</sup> Thiazides have been reported to increase glucose, uric acid, cholesterol, and triglyceride levels.<sup>32</sup> Beta blockers have been reported to cause unfavorable changes in lipid profiles.<sup>33</sup> In comparison, isradipine has been shown to be relatively free of biochemical abnormalities.<sup>11,16,17</sup>

**Serum glucose.** Mild increases in serum glucose levels were noted among isradipine-treated patients. The frequency of these was no more than among placebo-treated patients, and was less than among those who received HCTZ, propranolol, or prazosin.<sup>17</sup>

**Liver function.** Calcium channel blockers have been associated with liver function abnormalities. In clinical trials of isradipine, when there were abnormalities of liver function, they were transient and clinically insignificant.<sup>17</sup>

**Lipid profile.** Many antihypertensive agents have unfavorable effects on serum lipid levels.<sup>24</sup> The findings with isradipine have shown either a neutral or possibly a favorable effect on lipids. Samuel and colleagues demonstrated that short- or long-term isradipine ad-

ministration did not adversely affect serum lipid, lipoprotein, or apolipoprotein levels.<sup>34</sup> Long-term administration of HCTZ, on the other hand, resulted in significantly increased triglyceride levels.

Rauramaa and associates investigated the effects of isradipine and nifedipine on serum lipids, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) cholesterol and apolipoproteins AI and AII.<sup>24</sup> They found that the isradipine-treated group showed a significant increase in the HDL:LDL cholesterol ratio and a significant decrease in LDL levels. In addition, whereas nifedipine-treated patients showed increases in apolipoproteins AI and AII in the LDL plus VLDL fractions, isradipine showed increases of apolipoprotein AI and AII in the HDL fraction. The authors conclude that these findings suggest that isradipine has a favorable effect on lipid metabolism.

### Renal handling

The long-term effects of isradipine on renal hemodynamics and excretion in hypertensive patients were studied by Krusell and co-investigators.<sup>35</sup> They found that blood pressure and renal vascular resistance were significantly decreased, and there were slight increases in glomerular filtration rate and renal plasma flow. A significant increase in the clearance of sodium was also noted. These investigators also reported that in contrast to diuretics and beta blockers, isradipine caused a significant increase in uric acid clearance. Data from patients treated for two years with isradipine confirmed that renal function was preserved and that natriuretic and uricosuric actions were sustained.<sup>36</sup>

Persson and associates also studied the long-term effects of isradipine on renal hemodynamics.<sup>37</sup> Along with a decrease in diastolic blood pressure, they also found that renal plasma flow increased significantly, glomerular filtration rate remained unchanged, and the filtration fraction was significantly reduced. These investigators also found a repetitive postdose increase in natriuresis.

### Cardiac effects

In a study of hypertensive patients receiving oral isradipine, Winer and colleagues found no clinical evidence of depression of myocardial function, as indicated by signs or symptoms of congestive heart failure.<sup>19</sup> van den Berg and Dehmer recently studied the acute hemodynamic effects of intravenously administered isradipine.<sup>38</sup> In these patients receiving isradipine, cardiac index and stroke volume index both increased while myocardial oxygen consumption remained unchanged.

In a study of the electrophysiologic properties of isradipine administered intravenously, van Wijk et al found that in patients with normal SA and AV node function, isradipine did not cause negative SA or AV nodal effects.<sup>39</sup> In fact, isradipine seemed to help AV conduction. Subsequently, these investigators studied the effects in patients with sick sinus syndrome. Even in the presence of impaired sinus node function, isradipine was without negative SA or AV nodal effects.<sup>40</sup> Carr and Prisant found no significant changes in the ECG conduction parameters induced by isradipine among black hypertensive patients receiving the drug orally.<sup>23</sup>

In their study of hypertensive patients, Winer and colleagues found that chronic treatment with isradipine had no significant negative SA nodal effect.<sup>19</sup> The authors contrasted this with verapamil, which causes either no change or slight reduction in heart rate, and diltiazem, which causes slightly greater heart rate reduction. In addition, isradipine caused little or no prolongation of AV conduction time on serial ECGs, supporting the minimal effect of isradipine on AV conduction. In contrast, verapamil and diltiazem both prolong AV conduction time. Also in this study, supine heart rate returned toward baseline as blood pressure was reduced further with increasing doses of isradipine. This most probably was the result of the inhibitory effect of isradipine on sinus node impulse generation.<sup>19</sup>

Left ventricular hypertrophy (LVH), a result of chronic increased blood pressure, is a risk factor for cardiovascular morbidity and mortality. In a study of black hypertensive patients, Carr and Prisant found that isradipine monotherapy controlled blood pressure, decreased left ventricular wall thickness and mass, decreased ECG ST/T changes of ischemia, and improved left ventricular pumping ability.<sup>23</sup> In their review, Messerli and co-workers reported that short-term treatment with isradipine has been associated with a significant decrease in left ventricular mass in hypertensive patients.<sup>41</sup> This could be due to a decrease in intracellular calcium ions<sup>1</sup> or reduction in ventricular afterload.<sup>41</sup>

### Antiatherogenic effect

Of recent interest is the role of calcium channel

blockers in atherogenic disease. The changes caused by atherosclerosis may seriously impair both the integrity and function of the arterial wall, leading to loss of elasticity of the arterial wall, narrowing of the artery, and increased brittleness.<sup>42,43</sup>

In animals, calcium channel blockers such as nifedipine, verapamil, and diltiazem—when given in doses far in excess of the equivalent clinical therapeutic doses—reduce the progression of atherogenic lesions in experimentally-induced atherosclerosis by inhibiting the proliferation of early aortic lesions. In contrast, isradipine doses that are within the range of those relevant for human use showed antiatherogenic activity in the cholesterol-fed rabbit (the universal test model). Subsequent preliminary studies on extracellular matrix production (the matrix traps and binds plasma macromolecules such as LDL in the presence of calcium) have shown that isradipine, unlike other calcium channel blockers, has an inhibitory effect.<sup>42,43</sup>

Habib and colleagues showed that isradipine, even at doses that exerted no hypotensive effect in cholesterol-fed rabbits, partly prevented impairment of endothelium-dependent relaxation and reduced structural and biochemical changes of atherosclerosis.<sup>44</sup>

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### CONCLUSION

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Isradipine has been shown in controlled, double-blind, clinical trials to be an effective first-line monotherapeutic agent in the treatment of hypertension. Most patients responded to dosages of 5 mg to 15 mg per day, and, in general, there was no additional antihypertensive benefit at dosages greater than 10 mg per day. This antihypertensive agent has been well tolerated, with few adverse effects reported.

Isradipine has not been associated with common safety concerns of other calcium channel blockers in that it does not cause significant changes in cardiac conduction or the force of cardiac contraction. In addition, it does not adversely affect the lipid profile. Long-term experience indicates that the antihypertensive efficacy is maintained without tachycardia or tachyphylaxis.

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