Antihypertensive, Antiatherosclerotic, and Plasma Lipid-Lowering Effects of Monatepil, a Novel Calcium Antagonist With \( \alpha_1 \)-Adrenoceptor-Blocking Activity in Experimental Animals

Mizuo Miyazaki

Traditional antihypertensive therapy has been shown to reduce the incidence of hypertension-related vascular injuries; however, it is not fully effective against cardiovascular abnormalities. In some animal models, calcium antagonists have been demonstrated to possess antiatherogenic properties but to have no effects on plasma lipid levels, whereas \( \alpha_1 \)-adrenoceptor blockers have been shown to reduce plasma lipid levels. Monatepil is a new type of calcium antagonist that also has \( \alpha_1 \)-adrenoceptor-blocking activity. Therefore, it is thought that monatepil may have both antiatherosclerotic and plasma lipid-lowering effects in addition to its slow-onset and long-lasting antihypertensive effect.

To determine the antiatherosclerotic effects of monatepil, we examined its effect on experimental atherosclerosis induced by feeding a high-cholesterol diet to monkeys, whose lipid metabolism resembles that of humans. Monatepil, at a daily dose of 30 mg/kg, at which plasma levels are equivalent to those in clinical antihypertensive therapy, was administered orally for 6 months. Monatepil suppressed elevation of cholesterol in the aorta and reduced the atherogenic (sudanophilic) area. Histologic examination revealed that monatepil-treated monkeys exhibited little aggregation of foam cells in either the aorta or coronary arteries compared with vehicle-treated atherogenic monkeys.

In addition, monatepil showed preventive effects against increases in total cholesterol and low-density lipoprotein (LDL), and against decreases in high density lipoprotein in plasma caused by cholesterol loading.

The plasma lipid-lowering effect may be mediated through up-regulation of the number of hepatic LDL receptors by the \( \alpha_1 \)-adrenoceptor-blocking activity, and the antiatherosclerotic effect may be produced by the combined calcium antagonist, \( \alpha_1 \)-adrenoceptor-blocking, and antilipid peroxidation activities.

In summary, monatepil is an antihypertensive agent belonging to a new class with antiatherogenic properties and the ability to reduce plasma lipid levels. Am J Hypertens 1994;7:131S–140S

KEY WORDS: Calcium antagonist, \( \alpha_1 \)-adrenoceptor blocker, monatepil, antiatherosclerosis.
Hypertension is frequently associated with dyslipidemia, an important risk factor in atherosclerosis, and, in studies with experimental animals and human subjects, it has been shown to have some influence on the progression of atherosclerosis caused by hyperlipidemia. Recent progress in hypertension therapy has allowed many vascular complications attributable to abnormally high blood pressure to be prevented; however, prevention of atherosclerotic complications of hypertension, such as coronary artery disease, has not improved. This situation suggests that blood pressure reduction alone is not sufficient to prevent or treat cardiovascular complications. To achieve satisfactory results against atherosclerosis, hyperlipidemia and other risk factors need to be controlled.

The development of a novel antihypertensive drug that can reduce risk factors for coronary diseases would be welcomed. The effects of various antihypertensive drugs on lipid metabolism vary. Conventional drugs, such as thiazide diuretics and β-blockers, have been shown to have detrimental effects on lipid metabolism, whereas calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors have been demonstrated to have no adverse effects on lipid metabolism. On the other hand, α₁-adrenoceptor antagonists have been reported to be associated with favorable effects on lipid metabolism such as decreasing cholesterol and low density lipoprotein (LDL), and increasing high density lipoprotein (HDL) levels in plasma.

The antiatherosclerotic effects of conventional calcium antagonists have not yet been clinically defined despite the plethora of studies on antihypertensive drugs. However, there have been recent reports that calcium antagonists have promising antiatherosclerotic effects in experimental animals fed a high-cholesterol diet. At present, the therapeutic effectiveness and significance of conventional calcium antagonists are being investigated in several large-scale clinical studies. In contrast, α₁-adrenoceptor antagonists are known to have an effect against hyperlipidemia, which can prevent atherosclerosis when accompanied by blood pressure control.

<table>
<thead>
<tr>
<th>TABLE 1. INHIBITORY EFFECT OF VARIOUS DRUGS ON KCl-INDUCED VASOCONSTRICTION AND [¹⁴⁵Ca²⁺] UPTAKE OF ISOLATED RAT THORACIC ARTERY</th>
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</thead>
<tbody>
<tr>
<td><strong>Inhibition (IC₅₀ nmol/L)</strong></td>
</tr>
<tr>
<td>Monatepil</td>
</tr>
<tr>
<td>Vasoconstriction (relative value)</td>
</tr>
<tr>
<td>(1.00)</td>
</tr>
<tr>
<td>[¹⁴⁵Ca²⁺] uptake</td>
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IC₅₀: Concentration at which 50% of [¹⁴⁵Ca²⁺] uptake is inhibited.

Monatepil monomaleate (AJ-2615) [(±)-N-(6,11-dihydrodibenzo[b,e]thiepin-11-yl)-4-(4-fluorophenyl)-1-piperazinbutanamide monomaleate] (Figure 1) is a new type of antihypertensive agent. Its unique chemical structure was specially designed with intrinsic calcium antagonist and α₁-adrenoceptor-blocking moieties, creating a dual mechanism of action. Positive effects on plasma lipid metabolism are derived from the α₁-adrenoceptor-blocking activity and the antiatherosclerotic effect derives from the calcium antagonist properties. The novel structure of monatepil produces a slow onset of action and a long-lasting antihypertensive effect in experimental animals.

In this article, the pharmacologic profile and potential of monatepil in the treatment of hypertension are discussed.

CALCIUM ANTAGONIST ACTIVITY

Monatepil is a calcium antagonist that, as do existing calcium antagonists, inhibits the influx of extracellular Ca²⁺ through voltage-dependent Ca²⁺ channels. However, the binding site of monatepil is different from known binding sites of existing calcium antagonists (dihydropyridine, phenylalkylamine, and benzothiazepine). The calcium channel-blocking activity of monatepil (pA₂ value 8.71) is 20-fold more potent than that of diltiazem and about one-thirteenth less potent than that of nifedipine (Table 1).

The slow onset of the calcium antagonist activity of...
Monatepil has been demonstrated in isolated blood vessels; this activity is not washed out easily with bath medium. This high tissue affinity is believed to be one of the reasons for the slow, persistent antihypertensive action of monatepil (Figure 2).20

**α₁-ADRENOCEPTOR-BLOCKING ACTIVITY**

Monatepil, unlike existing calcium antagonists, potently inhibits the binding of [³H]-WB4101 to the α₁-adrenoceptor and also inhibits phenylephrine-induced vasoconstriction of isolated rabbit mesenteric artery. This inhibitory activity (IC₅₀ 39 nmol/L) is nearly equal in potency to its calcium antagonist activity (IC₅₀ 21 nmol/L).20

The hypotensive effect of monatepil in pithed rats is attenuated by 30% after prazosin pretreatment, suggesting that the α₁-adrenoceptor-blocking activity contributes to the antihypertensive activity.26 This blocking activity is probably involved in the plasma lipid-lowering effect of monatepil.

**ANTIHYPERTENSIVE EFFECT**

The antihypertensive effect of monatepil has been shown to be dose dependent with a slow onset and...
long duration in various hypertensive animal models (i.e., dogs and rats). The maximal potency is approximately equivalent to that of diltiazem, but less than that of nifedipine (Figure 3). Repeated once-daily oral administration of monatepil produces a stable antihypertensive effect and does not cause either tolerance or a rebound phenomenon after withdrawal. Furthermore, at the antihypertensive dose, monatepil did not have a significant effect on heart rate or the cardiac conduction system. At the time blood pressure was lowered, monatepil decreased total peripheral resistance, indicating a peripheral vasodilatory action.

ANTIATHEROSCLEROTIC AND PLASMA LIPID-LOWERING EFFECTS

High-Cholesterol Diet-Fed Monkeys Monatepil at a dose (30 mg/kg po for 6 months) at which the plasma concentration was almost the same as that observed in clinical studies inhibits increases in total cholesterol and LDL in monkeys (*Macaca fuscata*) fed a high-cholesterol diet (normal diet supplemented with 2% cholesterol and 6% corn oil) (Figure 4). However, prazosin (2 mg/kg twice daily) showed no significant suppressive effect on any plasma lipid except LDL (Figure 4). Monatepil also inhibits increases in cholesterol content in the abdominal and thoracic aorta (Table 2) and the progression of histopathologically observed atherosclerotic lesions (Figures 5, 6, and 7).

The antiatherosclerotic profile of monatepil is different from that of prazosin. Although histologic observations revealed intimal thickening in the aorta in cholesterol-fed control, prazosin-treated, and monatepil-treated groups, there was no aggregation of foam cells in the monatepil-treated group (Figure 8). Furthermore, coronary atheromatous lesions, one of the major manifestations of ischemic heart disease, were found in four of seven animals in the cholesterol-fed control group and in three of five animals in the prazosin-treated group. No atheromatous lesions were found in the monatepil-treated group (Figure 9).

On the basis of these results, we speculate that monatepil may have antiatherosclerotic and plasma lipid-lowering effects in clinical antihypertensive

### TABLE 2. EFFECT OF MONATEPIL AND PRAZOSIN ON CHOLESTEROL CONTENT OF THE AORTA

<table>
<thead>
<tr>
<th>Group</th>
<th>Thoracic Content of Aorta (mg/g wet weight)</th>
<th>Abdominal Content of Aorta (mg/g wet weight)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>4.6 ± 0.7*</td>
<td>2.4 ± 0.2*</td>
</tr>
<tr>
<td>HCD</td>
<td>19.0 ± 2.8</td>
<td>7.3 ± 0.9</td>
</tr>
<tr>
<td>HCD + monatepil</td>
<td>8.8 ± 1.1*</td>
<td>3.4 ± 0.3*</td>
</tr>
<tr>
<td>HCD + prazosin</td>
<td>14.5 ± 2.7</td>
<td>5.9 ± 1.1</td>
</tr>
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</table>

HCD, High-cholesterol diet-fed animals. *P < .05 and **P < .01 indicate that the sudanophilic area is significantly different from that of a high-cholesterol diet-fed monkey. The area of a sudanophilic lesion is expressed as a percentage calculated as sudanophilic area/total intimal area × 100.
FIGURE 6. Gross appearance of thoracic aorta stained with Sudan IV. (A) Normal diet control; (B) high-cholesterol diet-fed control; (C) monatepil (AJ-2615) (30 mg/kg daily); (D) prazosin (2 mg/kg twice daily). Reproduced with permission from Miyazaki et al.27
FIGURE 7. Gross appearance of abdominal aorta stained with Sudan IV. (A) Normal diet control; (B) high-cholesterol diet-fed control; (C) monatepil (AJ-2615) (30 mg/kg daily); (D) prazosin (2 mg/kg twice daily). Reproduced with permission from Miyazaki et al.²⁷
therapy, although definitive clinical studies have not been performed.

**High-Cholesterol Diet-Fed Rabbits**  The antiatherosclerotic and plasma lipid-lowering effects of monatepil and existing calcium antagonists have been compared in rabbits fed a high-cholesterol diet (normal diet supplemented with 1% cholesterol and 6% coconut oil). Monatepil (30 mg/kg) daily for 9 weeks significantly suppressed increases in plasma cholesterol and phospholipids at week 4 or 6 of treatment and thereafter. On the other hand, prazosin (3 mg/kg twice daily), diltiazem (50 mg/kg twice daily), and the combination of these two drugs showed no inhibitory effect. Monatepil significantly suppressed increases in total cholesterol, phospholipid, and calcium content, and the atherosclerotic lesion area in the isolated aorta. Prazosin and diltiazem administered separately caused no significant decrease, but when combined significantly decreased calcium content and tended to inhibit the progression of atherosclerotic lesions in rabbit aorta.

**Mechanisms of Plasma Lipid-Lowering Effects**  Conventional calcium antagonists are known to lack effects on plasma lipid levels. Thus, if monatepil were a conventional calcium antagonist, it would follow that monatepil does not prevent hyperlipidemia; however, monkey and rabbit studies have shown that monatepil decreases plasma lipids and lipoprotein levels.

What is the mechanism of this apparent plasma lipid-lowering effect? One possibility is up-regulation of hepatic LDL receptor expression at the genetic level in high-cholesterol diet-fed monkeys. After cholesterol loading, the concentration of LDL receptor mRNA is decreased to 30% of that in monkeys fed a normal diet. However, monatepil up-regulates LDL receptor mRNA concentration, restoring it to the normal level (three- to fourfold stimulation). These results strongly suggest that monatepil increases the number of LDL receptors in the liver and subsequently lowers plasma LDL.

The up-regulation of hepatic LDL receptor-mediated lipid metabolism is thought to be derived...
from the \(\alpha_1\)-adrenoceptor-antagonist activity of monatepil. Doxazosin, an \(\alpha_1\)-adrenoceptor blocker, has also been reported to up-regulate lipid metabolism through LDL receptors in HepG2 cells.\(^{30}\) Monatepil, like doxazosin, suppresses phenylephrine-induced vasoconstriction,\(^{20}\) suggesting a similarity in the \(\alpha_1\)-adrenoceptor-blocking activity. It has been reported that doxazosin also inhibits the synthesis of endogenous cholesterol by suppressing HMG-CoA reductase activity,\(^{31}\) therefore, monatepil may also inhibit HMG-CoA reductase activity.

**Mechanisms of the Antiatherosclerotic Effect** As with the plasma lipid-lowering effects, there are several mechanisms of action speculated to be responsible for the antiatherosclerotic effects of monatepil. One theory is that the blood pressure-lowering activity affects the atherogenic process. The close relation between shear stress and the development of atherosclerotic lesions is well known and could suggest that the blood pressure-lowering effect of monatepil plays a part in its antiatherosclerotic effects. However, nifedipine is unable to prevent atherosclerosis despite its potent hypotensive activity.\(^{32}\) Moreover, in a study on normotensive monkeys, monatepil did not significantly affect blood pressure. In effect, blood pressure lowering does not play an important role in the antiatherosclerotic effect of monatepil.

The relation between calcium and atherosclerosis is also well known and the preventive effects of various calcium antagonists against atherosclerosis have been studied in experimental\(^{33,35}\) and clinical studies.\(^{36-38}\) Monatepil shows calcium antagonist activity with a potency similar to that of conventional calcium antagonists.\(^{20}\) This indicates that monatepil could have mechanisms of action similar to those of existing calcium antagonists, suppression of atherogenic platelet dysfunction,\(^{12}\) and inhibition of chemotaxis,\(^{39}\) cell migration,\(^{39}\) cell proliferation,\(^{40,41}\) deposition of matrix protein,\(^{42}\) and tissue mineralization.\(^{43}\)

Another possible mechanism is inhibition of the increase in plasma lipid peroxide, an index of antioxidation, by monatepil. Monatepil exerts an inhibitory effect on lipid peroxide formation in the mitochondria of the rat heart that is 0.25-fold that of probucol and about twofold that of vitamin E.\(^{28}\) The antiatheroscle-
Various in vivo experiments have demonstrated that monatepil exerts an antihypertensive effect of slow onset and long duration that permits a once-daily dosing regimen. However, it has virtually no effect on the cardiac conduction system or on heart rate. Antithrombotic and plasma lipid-lowering effects have been observed in various animal disease models; these effects are believed to be due to the calcium antagonist, α₁-adrenoceptor-blocking, and antilipid peroxidation activities of monatepil.

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REFERENCES


