Benidipine: A New Ca$^{2+}$ Channel Blocker with a Cardioprotective Effect


Department of Internal Medicine and Therapeutics, Osaka University School of Medicine, Suita, Japan, *Drug Discovery Research Laboratories, Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co., Ltd., Sunto, Shizuoka, Japan, and †Toxicological Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., Ube Yamaguchi, Japan

Key Words: Dihydropyridine—Ca$^{2+}$ channel blockers—Slow-onset action—Long-acting effects—High lipid solubility—Vascular selectivity—Cardioprotection—Nitric oxide—Myocardial ischemia—Hypertension—Obesity—Insulin—Lipolysis.

INTRODUCTION

Ca$^{2+}$ channel blockers are widely used for the treatment of ischemic heart disease and systemic hypertension because of their ability to effectively dilate coronary and systemic arteries (30,44). Ca$^{2+}$ channel blockers increase coronary blood flow (CBF) in inhibiting Ca$^{2+}$ entry into smooth muscle cells (48). Since Ca$^{2+}$ overload is deleterious for the maintenance of cellular homeostasis, Ca$^{2+}$ channel blockers are believed to be effective in attenuating Ca$^{2+}$ overload. However, Ca$^{2+}$ overload in ischemic and hypoxic cardiomyocytes is reportedly mediated by Na$^+$/H$^+$ and Na$^+$/Ca$^{2+}$ exchangers, not by Ca$^{2+}$ channels. Thus, Ca$^{2+}$ channel blockers may not attenuate Ca$^{2+}$ overload during myocardial ischemia and reperfusion. Recently, it has been reported that benidipine can protect endothelial cell function in the renal resistance arteries of hypertensive rats (3) and the mesenteric arteries of rats subjected to circulatory shock (20). Endothelial cell function is important for the preservation of organ function during ischemic or hypertensive stress (1,32,42). Indeed, endothelial-dependent coronary vasodilation is impaired in patients with either coronary artery disease or systemic hypertension, both of which reduce the levels of nitric oxide (NO). Benidipine reportedly has a cardioprotective effect during myocardial ischemia and reperfusion injury (6). Since myocardial ischemia impairs endothelial cell function by the activation of platelets and leukocytes (4,59), benidipine may attenuate endothelial cell dysfunction and increase the production of nitric oxide in ischemic hearts.

We describe here the clinical, pharmacological, and cardiovascular properties of benidipine and the role of NO in benidipine-induced cardioprotection.

Address correspondence and reprint requests to Dr. M. Kitakaze, M.D., Ph.D., Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Japan 565-0871. Fax: 81-6-6879-3645.
CHEMISTRY AND MECHANISMS OF ACTION

Benidipine hydrochloride, (±)-(R*)-3-[(R*)-1-benzyl-3-piperidyl] methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridine dicarboxylate hydrochloride (KW-3049), is a racemic mixture of two isomers [(S)-(S)-(+)] and [(R)-(R)-(-)] (34) (Fig. 1). It was developed as a long-acting, L-type Ca\(^{2+}\) channel blocker. As a solid, benidipine is stable to variations in heat and moisture, and is fairly stable to light exposure (54). In vivo benidipine has a slow onset of action. The racemate nature of benidipine seems to play a role in this slow-onset antihypertensive effect, which results in minimal tachycardia or palpitation. In the clinical setting, this property is very important in the treatment of heart disease, because it is undesirable to induce acute systemic hemodynamic changes in patients with ischemic or failing hearts.

The vasorelaxant effect of benidipine is attributable to high affinity dihydropyridine binding sites (i.e., the binding site in Ca\(^{2+}\) channels). The \(K_i\) values are 0.13 and 0.08 nM/mL in the cerebrum and heart membranes, respectively (12,13). Benidipine associates with and dissociates from its binding site at a very slow rate (16). Its slow kinetics was also shown in isolated coronary arteries (43). This property seems to be related at least in part to a high lipid solubility. The partition coefficient of this drug in the octanol/buffer system and synaptic membranes are 6,460 and 16,500 (53), respectively, indicating that benidipine preferentially distributes to the bipolar lipid layer of the cell membrane (8). Therefore, benidipine can readily approach Ca\(^{2+}\) channels in cell membranes of target cells from within the membrane (i.e., the membrane approach). Indeed benidipine inhibits Ca\(^{2+}\) current when applied from either side of the patch pipette during whole cell patch clamping (3).

TOXICITY

Benidipine toxicity was assessed in vivo in mice, rats, guinea pigs, rabbits, and dogs and in vitro in CHL cells and bacteria. In acute toxicity studies, the \(LD_{50}\) values of benidipine were 321.6 and 384.5 mg/kg, p.o., in male and female mice, respectively. Rats were also

\[
\begin{align*}
\text{Fig. 1. Chemical structure of benidipine.}
\end{align*}
\]
sensitive to acute toxicity and there was a sex difference between males and females (LD$_{50}$: 87.6 and 197.9 mg/kg, p.o., respectively). Subacute toxicity was examined in rats by daily oral administration at doses of 3, 6, 25, 50, and 100 mg/kg/d for 3 mo. We observed fatty changes of the liver and an increase in the weight of the heart, which was slightly larger in female rats. Dose-dependent reversible fat deposits in the peripheral and intermediary zones of the hepatic lobules were observed. Low doses (0.38, 1.5, and 3 mg/kg/d, p.o.) of benidipine did not increase heart weight after 3 mo of administration. In chronic toxicity studies in rats, benidipine was administered orally for 12 mo. Heart weight increased only at the pharmacological dose (1.5 mg/kg/d). The weight of the thymus decreased with doses of benidipine >0.75 mg/kg/d.

Subacute toxicity studies with daily oral administration of the drug at doses of 1.5, 3, 6, and 12 mg/kg/d for 3 mo were performed in dogs. The heart rate and heart weight increased with doses of 1.5 mg/kg/d or more, and atrioventricular block was observed in dogs administered 6 mg/kg/d. However, there were no noticeable histopathological changes in the heart. In another experiment using lower doses (0.17, 0.5, and 1.5 mg/kg/d, p.o.) of drug administered for 3 mo, benidipine had no effect on heart rate or weight. When the duration of drug administration in dogs was extended to 12 mo, gingival hypertrophy (at 1.5 mg/kg/d or more), increased heart rate and weight (at 1.5 mg/kg/d or more), and atrioventricular block (at 6 mg/kg/d) were observed. In gingiva, elongation and reticular formation of the rete ridges, subepidermal inflammatory cell infiltration (at 0.38 mg/kg/d or more), and subepidermal fibroplasia (at 1.5 mg/kg/d) were observed. However, at the dose of 0.38 mg/kg/d, histological changes were less frequent and less marked than in control animals. A different set of 12-mo experiments (at doses of 0.75, 1, and 1.5 mg/kg/d) indicated that 1.5 mg/kg/d benidipine is the minimum dose that induces macroscopic and microscopic gingival hypertrophy.

Teratogenicity studies in rats and rabbits showed no malformations in any group. Fertility studies in rats showed no noticeable difference from control animals except for a very slight decrease in the number of corpora lutea in animals administered 50 mg/kg. Perinatal and postnatal studies in rats (6, 12, 25, and 35 mg/kg, p.o.) showed that body weight gain was suppressed, death occurred sporadically, the pregnancy period (at doses of 25 and 35 mg/kg) and delivery time were prolonged, and the number of stillborn fetuses was increased. The results of various tests of antigenicity, mutagenicity, and carcinogenicity were all negative, although some Ca$^{2+}$ channel blockers are thought to be related to carcinogenicity, as determined by a clinical meta-analysis. We conclude that benidipine is a safe drug with a wide safety dose range.

**PHARMACOKINETICS AND METABOLISM**

The absorption, metabolism, and excretion of [1$^{4}$C]benidipine hydrochloride were determined following oral administration to healthy male Caucasian volunteers at a dose of 8 mg (25). [1$^{4}$C]benidipine was rapidly absorbed, and the plasma concentration of the unchanged drug reached a maximum of 71.2 ng/mL at 1.1 h and 2.56 ng/mL at 0.6 h, respectively, and then declined biexponentially. The area under the concentration curve of the unchanged drug represented ~1% of the radioactivity. Up to 5 d after administration, 36.4% of the radioactivity was excreted in urine and 58.9% in feces. Benidipine was extensively metabolized. One hour after administration, the predominant metabolites in
plasma were M9 and M2 (Fig. 2) (27), accounting for 13.8 and 8.2% of the radioactivity, respectively, whereas unchanged drug represented 1.2%. Predominant metabolites in urine 12 h after administration were M3 and M8, accounting for 2.22 and 2.21% of the administered radioactivity, respectively. Excretion of unchanged drug was negligible.

Benidipine was rapidly absorbed after oral administration in healthy fasting male Japanese volunteers at doses of 2, 3, 8, and 12 mg (Fig. 3) (58). The $C_{\text{max}}$ was 0.55, 2.25, 3.89, and 10.81 ng/mL, respectively. Thereafter, the plasma concentration decreased almost monoexponentially with a half-life of 1–3 h. Benidipine’s pharmacokinetics was linear in this dose range. A delay in the rate of absorption of benidipine and an increase in the area under the concentration curve (ca. 1.63 times compared with the fasting state) was observed after oral administration to healthy volunteers at a dose of 8 mg in the post-prandial state. The $C_{\text{max}}$ value was 1.26 times higher in the fasting state (personal communication, Uji Y., Tokyo Musashino Hospital affiliated with the Seishin-Igaku Institute, Tokyo, Japan). The plasma concentration-time profile of orally administered benidipine (4 mg dose) was affected by the concomitant intake of grapefruit juice. The $C_{\text{max}}$ value increased 1.98 times and the area under the concentration curve was 2.12 times higher when compared with concomitant intake of water.

Counterclockwise hysteresis between plasma concentration and a decrease in systolic blood pressure was found after oral administration of benidipine in patients with essential hypertension (37). This relationship can be explained by application of the effect compartment model or ion-channel binding model (52) to understand the long-acting pharmacological activity of benidipine. Slow dissociation of benidipine from the calcium channels, expected from the small dissociation constant in the in vitro binding studies, could explain its long duration of action.

**CARDIOHEMODYNAMIC EFFECTS**

Although benidipine is a dihydropyridine Ca$^{2+}$ channel blocker, the cardiohemodynamic effects of this drug are quite different from other Ca$^{2+}$ channel blockers (55). First, pharmacological activity appears gradually and persists for a long time following oral administration. This property is necessary for benidipine to exert its maximal cardioprotective effect, because activation of the sympathetic and renin-angiotensin systems, both of which are deleterious to the diseased heart, are avoided. Indeed, amlodipine, a long acting Ca$^{2+}$ channel blocker, was recently reported to attenuate mortality of patients with non-ischemic chronic heart failure (45), and a long-acting formulation of nifedipine was shown to attenuate mortality due to cardiovascular and cerebral diseases in elderly patients with essential hypertension (7). In contrast, short-acting Ca$^{2+}$ channel blockers are not as cardioprotective. Second, benidipine selectively dilates the vasculature with minimal effect on cardiac contractility (16,18). Third, benidipine has potent antihypertensive effects (3,26,36). When patients with essential hypertension are treated with benidipine, the daily variability of systemic blood pressure is minimized and the nocturnal decline of blood pressure is not observed following a once-a-day dosage regimen (35). Via a reflex mechanism, most Ca$^{2+}$ channel blockers induce tachycardia and a marked elevation of plasma catecholamines (i.e., neurohumoral activation) that increase the risk of adverse cardiac events (9). In contrast, benidipine elevates plasma catecholamine levels only slightly.
FIG. 2. Proposed metabolic pathways of benidipine. Benidipine was rapidly absorbed after oral administration in healthy fasting male Japanese volunteers at doses of 2, 4, 8, and 12 mg. \( C_{\text{max}} \) values were 0.55, 2.25, 3.89, and 10.81 ng/mL, respectively. Thereafter, benidipine was eliminated from the plasma almost monoexponentially with a half-life of 1–3 h. Pharmacokinetics of benidipine were linear in the range of these doses. From Ref. 27.
Consequently, reflex tachycardia is less prominent with benidipine when compared with vasodilators that exhibit a rapid onset of action. Moreover, elevation of plasma norepinephrine is reversed within 2 w following chronic treatment of hypertensive patients with benidipine (5). Benidipine is also a potent vasodilator of the coronary, cerebral, and renal vasculature (17). Both in vitro and in vivo experiments have shown that vascular selectivity of benidipine is quite high (16,18,33) and that benidipine is more selective than nifedipine or amlodipine. The selectivity ratio of benidipine and amlodipine for the canine coronary artery and papillary muscle are 1300 and 67, respectively (33). This property of benidipine may be especially advantageous in elderly patients who often exhibit cardiac dysfunction.

PROTECTIVE EFFECTS ON THE ENDOTHELIUM

One of the distinguishing characteristics of benidipine is its protective effect on the endothelium. In several experimental models of endothelial cell damage, benidipine was shown to protect the endothelium from injury. Benidipine prevents endothelial cell dysfunction following ischemia and reperfusion of the cardiac and visceral arteries (22,60), and it ameliorates endothelial cell degeneration induced by challenge with toxic chemicals such as sodium citrate or vitamin D₃ plus nicotine (10,50).

Benidipine has been shown to exhibit prominent protective effects against ischemic damage in the heart and brain (10,15,19,50,57,60). These protective effects may be due to either an inhibitory effect against Ca²⁺ overload, selective vasodilation, or a protective effect on the endothelium. We have recently reported a novel finding that benidipine attenuates the extent of ischemia through NO-dependent mechanisms (23). In anesthetized dogs, a proximal portion of the left anterior descending coronary artery (LAD) was
cannulated and perfused with blood from the left carotid artery through an extracorporeal bypass tube. Benidipine, first administered into the LAD, was shown to increase levels of nitrate and nitrite in coronary venous blood, compared with arterial blood ($\Delta VA\text{[NO]} \times (3.9 \pm 0.7 \text{ nmol/mL at control,} 4.9 \pm 0.6 \times \text{[P < 0.05 vs. control],} 5.8 \pm 0.6 \times \text{[P < 0.05],} 7.2 \pm 0.6 \times \text{[P < 0.05] and} 7.1 \pm 0.3 \text{ nmol/mL [P < 0.05 during intracoronary infusion of 25, 50, 100, and 200 ng/kg/min benidipine, respectively]. However, benidipine did not affect the levels of adenosine in coronary venous blood relative to arterial blood. This is because Ca$^{2+}$ channel blockers reportedly inhibit adenosine uptake into cells and increase interstitial adenosine levels, which may induce coronary vasodilation. Benidipine increased CBF dose-dependently (Fig. 4), an effect that was partially attenuated by a NO synthase inhibitor (L-NAME, L$^\text{N}$-nitro arginine methyl ester), but not by an adenosine receptor antagonist (8-SPT, 8-sulfophenyltheophylline).

We then examined the effects of benidipine on the ischemic heart. Coronary perfusion pressure (CPP) was reduced with an occluder attached at the extracorporeal bypass tube such that CBF was decreased to 33% of the control level. After a low CPP was obtained, the occluder was adjusted to maintain a constant CPP. Benidipine increased $\Delta VA\text{[NO]}$, and in accordance with this effect, benidipine increased coronary blood flow (CBF) despite the constant CPP (Fig. 5). Fractional shortening (FS), an index of regional myocardial contraction, and lactate extraction ratio (LER), an index of myocardial anaerobic metabolism, were reduced after the onset of coronary hypoperfusion but increased following benidipine administration. These beneficial effects on the ischemic heart were attenuated by L-NAME. Since increased CBF may increase shear stress in coronary arteries, which may secondarily increase cardiac NO levels in ischemic hearts, we tested the effects of benidipine on cardiac NO levels under constant low CPP. Under these conditions, benidipine increased $\Delta VA\text{[NO]}$, and this effect was again attenuated by L-NAME. Benidipine decreased CPP due to coronary vasodilation and this effect was also prevented by L-NAME. Finally, we determined whether benidipine increased the cyclic GMP content of epicardial arteries in ischemic myocardium (23). The results indicated that benidipine increases cardiac NO levels in ischemic hearts; the NO in turn mediates coronary vasodilation and attenuates the severity of myocardial ischemia.

Because it was reported that amlodipine also increases NO levels in canine coronary microvessels (63), the ability to enhance the effects of NO may not be a unique property of benidipine, but may be common to all dihydropyridine Ca$^{2+}$ channel antagonists. However, the potency of this effect may be different for different Ca$^{2+}$ channel antagonists. Indeed, in preliminary studies we have observed that nifedipine also increases cardiac NO levels in ischemic hearts to the same levels as benidipine. Since Ca$^{2+}$ channel blockers can inhibit adenosine uptake into cells (29,47), and adenosine is a very potent coronary vasodilator (11), we first thought that adenosine-mediated mechanisms might be involved in benidipine-induced coronary vasodilation. Our data do not support this hypothesis. Instead we observed that NO-dependent mechanisms were involved in benidipine-induced coronary vasodilation. However, the extent of the involvement of NO in benidipine-induced coronary vasodilation in ischemic and non-ischemic hearts is quite different (Figs. 4 and 5). There are three possible explanations for this effect. First, if the probability that Ca$^{2+}$ channels are open in coronary artery smooth muscle is higher in non-ischemic hearts than in ischemic hearts, the ability of Ca$^{2+}$ channel blockers to inhibit Ca$^{2+}$ channels may be high enough to blunt the benidipine-induced NO-dependent coro-
nary vasodilation in non-ischemic hearts. On the other hand, if myocardial ischemia decreases the probability of open Ca^{2+} channels, benidipine may be unable to cause further coronary vasodilation by antagonism of Ca^{2+} channels. Thus, the relative importance of NO-dependent coronary vasodilation may increase. Indeed, endothelial-dependent hyperpolarization factor (EDHF) is released in the ischemic myocardium (39, 40, 51), and EDHF may hyperpolarize the cell membrane and decrease the probability of open Ca^{2+} channels in coronary artery smooth muscle in ischemic hearts. Secondly, since ischemia per se activates NO synthase by endogenous neurohumoral substances such as catecholamines, bradykinin, and adenosine, benidipine may further increase the activity of

FIG. 4. Changes in CBF during intracoronary administration of benidipine with and without L-NAME or 8-SPT. Statistical analysis was performed by ANOVA followed by Bonferroni’s test. From Ref. 23.
NO synthase that has already been partially activated. Considering that the dose-response curves are generally sigmoidal, the extent of the increase in NO synthase may be augmented in ischemic hearts compared with non-ischemic hearts during benidipine infusion. Thirdly, benidipine’s ability to increase cardiac NO levels may be greater under the ionic and neurohumoral conditions that develop in ischemic hearts. There are several stimuli that facilitate NO production. Foremost is benidipine’s reported ability to activate kallikrein in the kidney (61), which may increase bradykinin production in the heart. Indeed, it has been reported that NO-dependent vasodilation by amlodipine is partially attributable to bradykinin (63). Benidipine can increase production of EDHF as well as NO, and activate Ca²⁺-activated K⁺ channels (39,40,51), which may contribute to the cardioprotective effect (40).

We do not know whether other dihydropyridine Ca²⁺ channel blockers can increase NO levels as benidipine does. We have preliminary data indicating that nifedipine can also increase cardiac NO levels in ischemic hearts, suggesting that the effects of benidipine on NO levels may be a common characteristic of dihydropyridine Ca²⁺ channel blockers (unpublished observation). However, because benidipine has a high affinity for cell membranes where endothelial cell NO synthase is located, benidipine may be more potent than nifedipine in increasing cardiac NO levels. Further studies are required to resolve this issue.

ROLE OF NITRIC OXIDE IN ISCHEMIC AND HYPERTENSIVE HEARTS

Evidence is accumulating in support of the hypothesis that the effects of benidipine on the cardiovascular system are at least partly attributable to NO. Nitric oxide is believed to attenuate the severity of myocardial ischemia since it increases CBF, attenuates myocardial anaerobic metabolism, inhibits platelet aggregation and leukocyte activation, and attenuates the activation of sympathetic activity in ischemic hearts. The inhibition of NO
by L-NAME attenuates coronary vasodilation in the ischemic heart (Fig. 7; 24) and inhibition of NO production increases myocardial contraction induced by either isoproterenol or Ca\(^{2+}\). This effect is blunted by L-arginine (41). Interestingly, we have reported that a cardioprotective agent and an inhibitor of angiotensin converting enzyme, cilazaprilat, increased CBF via NO-dependent mechanisms in the ischemic canine heart (22). Since the activity of benidipine is also associated with NO-dependent mechanisms (23), benidipine may have additional benefit in the treatment of cardiac ischemia when compared to other Ca\(^{2+}\) channel antagonists.

NO also reportedly mediates cardioprotection during the late phase of ischemic preconditioning. Twenty-four or forty-eight hours after a brief period of ischemia, NO mediates the infarct size-limiting effects (2,28) or the attenuation of myocardial stunning (46), and these effects are blunted by L-NAME. Indeed, cardioprotection during the second window of ischemic preconditioning is blunted when knockout mice lacking inducible NOS are used for ischemic preconditioning. Taken together, the data support the idea that benidipine mediates or enhances NO-dependent cardioprotection in diseased hearts.

We have reported that NO levels in systemic blood are decreased in patients with hypertension (42) and it has been observed that chronic inhibition of NO synthase in the rat causes myocardial hypertrophy and fibrosis, coronary vascular stenosis, and hypertension. These histological changes, attributed to inhibition of NO synthase, are not prevented by an effective dose of hydralazine used in the treatment of hypertension (31,56). These results indicate that endogenous NO can inhibit both cardiac hypertrophy and coronary vascular remodeling. In preliminary studies, we have reported that p70 S6 kinase, which mediates protein synthesis, is activated in NO-depleted hearts (31). Since the effects of NO are attenuated in patients with essential hypertension, replacement of

FIG. 6. Dose-response curves to acetylcholine in renal resistance arteries with endothelium obtained from 26-w old WKY, untreated SHR, and benidipine- or ecarazine-treated SHR. Responses to acetylcholine were obtained in arteries contracted with each EC\(_{50}\) value of norepinephrine for the contraction (1.2 × 10\(^{-7}\) mol/L, left panel) or with 40 mmol/L KCl (right panel). Data are expressed as mean ± S.E.M. Note that long-term treatment with benidipine but not ecarazine normalized the impaired relaxation in SHR. From Ref. 3.
FIG. 7. Changes in coronary perfusion pressure (A), coronary blood flow (B), and fractional shortening (C) during the infusion and withdrawal of L-NMMA, an inhibitor of NO synthase before and during coronary hypoperfusion. Three to 5 min after the L-NMMA infusion, coronary blood flow gradually decreased (B), as did fractional shortening (C). The reduced coronary perfusion pressure was maintained at a constant level (A). From Ref. 24.
NO as well as normalization of high blood pressure may be necessary for the treatment of hypertension. Thus, benidipine may be more effective in the treatment of hypertension than other Ca\(^{2+}\) channel blockers or other antihypertensive drugs, since it can restore NO-dependent cell signaling as well as normalize systemic blood pressure. In renal hypertensive rats, benidipine also reversed cardiac hypertrophy and improved coronary flow reserve and microvascular remodeling (21). In addition, benidipine has been shown to attenuate endothelial dysfunction that accompanies systemic hypertension (Fig. 6; 3). Although the precise mechanism for the unique endothelial protective effect of this drug is still obscure, its antioxidant action (Kikuchi K et al., Personal Communication) combined with its high lipid solubility and inhibitory effect on Ca\(^{2+}\) overload, might be involved in the protective effect.

Finally, obesity, which may cause or be associated with hyperinsulinemia, has a detrimental effect on the cardiovascular system. Interestingly, benidipine may have an anti-obesity effect. In a mouse model of obesity induced by monosodium-L-glutamate, benidipine prevents obesity without affecting food consumption (62). In this mouse obesity model, benidipine activated brown adipose tissue, presumably by increasing the blood flow to this tissue (14). In rats, chronic treatment with benidipine for 50 w induced a decrease in visceral fat and body weight without affecting food intake, and it did not adversely influence the plasma lipid profile (49). It has not been clarified whether NO-dependent mechanisms are involved in the lipolytic effect induced by benidipine or whether the lipolytic effect is limited to benidipine or is shared with other Ca\(^{2+}\) channel blockers. Since adenosine can induce lipolysis in adipose tissue, inhibition of adenosine uptake by Ca\(^{2+}\) channel blockers may be involved (29,47), although we found that benidipine does not increase adenosine levels in the heart (23).

**SUMMARY**

Compared with other Ca\(^{2+}\) channel blockers, benidipine, a new dihydropyridine Ca\(^{2+}\) channel blocker, has been recently reported to have several unique properties. First, benidipine *per se* has a slow onset of action and long-acting effects *in vivo*, resulting in minimal sympathetic activation. Second, benidipine has a high lipid solubility, which suggests that it may interact from within the membrane with Ca\(^{2+}\) channels in the cell membrane of target cells. Third, the vascular selectivity of benidipine is very high compared with the other Ca\(^{2+}\) channel blockers, which may be especially advantageous in treating patients with cardiac dysfunction. Fourth, benidipine attenuates endothelial cell injury. Indeed, we have recently found that benidipine increases cardiac NO levels during myocardial ischemia in dogs (23). Taken together, these data suggest that benidipine may be a potent primary drug for the treatment of cardiovascular diseases that exerts its effect, at least in part, by enhancing NO-dependent mechanisms.

**Acknowledgments:** Supported by Grants-in-aid for Scientific Research (No. 10557068 and 10670649) from the Ministry of Education, Science, and Culture, Japan, and in part by a grant from the Smoking Research Foundation in Japan.

**REFERENCES**

28. Li WJ, Kitakaze M, Minamino T, Noda K, Hori M. Nitric oxide opens the second window of cardio-


