*New Drugs and Recent Techniques***Pharmacological, Pharmacokinetic, and Clinical Properties of Benidipine Hydrochloride, a Novel, Long-Acting Calcium Channel Blocker**Kozo Yao¹, Ken Nagashima^{2,*}, and Hiroyuki Miki³¹Department of Pharmacology and Molecular Biology, Pharmaceutical Research Center, Kyowa Hakko Kogyo Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8731, Japan²Pharmaceutical Marketing Center, Kyowa Hakko Kogyo Co., Ltd., 1-6-1 Ohtemachi, Chiyoda-ku, Tokyo 100-8185, Japan³Pharmaceuticals Division, Beijing Office, Kyowa Hakko Kogyo Co., Ltd., Beijing Fortune Bldg., Room 620, No. 5 Dong San Huan Beilu, Chao Yang District, Beijing 100004, People's Republic of China

Received April 5, 2005; Accepted February 8, 2006

Abstract. Benidipine is a dihydropyridine-derived calcium channel blocker developed in Japan, with several unique mechanisms of action, that is, triple calcium channels (L, N, and T) blocking action with a membrane approach. Benidipine has relatively high vascular selectivity and is expected to show protective effects on vascular endothelial cells. Renal protective effects of benidipine also have been shown in several basic and clinical studies. Moreover, anti-oxidative action and enhancing nitric oxide production have been noted with this drug, following its cardio-protective effects in patients with ischemic heart diseases. In fact, benidipine exerted a better prognostic effect than other calcium channel blockers in the therapy for patients with vasospastic angina. In addition, benidipine showed reliable antihypertensive, renoprotective effects if used in combination with angiotensin II type 1 receptor blockers (ARBs) when adequate anti-hypertensive effects are not achieved by ARBs alone, indicating that benidipine is an useful calcium channel blocker in combination therapy for hypertension. Benidipine was launched on the Japanese market 14 years ago, but few severe side effects have been reported, suggesting that this is a drug with established safety and long-acting pharmacological effects.

Keywords: benidipine, calcium channel blocker, hypertension, angina pectoris, membrane approach

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Published online in J-STAGE: March 25, 2006

DOI: 10.1254/jphs.DTJ05001X

1. Introduction

Hypertension is a major disease leading to cardiovascular diseases, and has become a common medical and social problem. In Japan, the number of patients with hypertension is estimated to be about 7-million, and the number of potentially hypertensive individuals is estimated to exceed 30 million on the basis of data collected by the Fifth National Basic Survey of Cardiovascular Diseases in 2000 conducted by the Ministry of Health, Labor, and Welfare (MHLW). As the number of aged persons have been increasing in Japan, the number of hypertensive individuals will further increase. The number of patients with angina pectoris is currently estimated to be about 2.6 million, and this number is also expected to increase in the future. It is now very important to facilitate the early diagnosis and treatment of cardiovascular diseases such as hypertension and angina pectoris.

The first study of calcium channel blockers (CCBs) was reported in 1969 by Fleckenstein et al. who demonstrated that the inhibition of calcium influx into cells led to compromised cardiac function (1). Currently, about 40 years after this report, CCBs are the most frequently used class of drugs in the treatment of cardiovascular diseases such as hypertension (2) and angina pectoris (3). In Japan, more than a dozen CCBs, particularly those with dihydropyridine (DHP) derivatives, have been launched on the market. These CCBs have various properties in terms of 1) anti-hypertensive and vasodilative effects, 2) the duration of these effects, 3) the profiles of organ-protective effects, and 4) the incidence of adverse effects. It is therefore necessary to understand the feature of each CCB.

Benidipine hydrochloride (benidipine, $(\pm)$ -(*R*^{*})-3-[(*R*^{*})-1-benzyl-3-piperidyl]methyl-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridine dicarboxylate hydrochloride, CAS 91599-74-5, KW-3049, Coniel[®]

Fig. 1. Chemical structure of benidipine hydrochloride: $(\pm)$ -(*R*^{*})-3-[(*R*^{*})-1-benzyl-3-piperidyl]methyl-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridine dicarboxylate hydrochloride.

tablets, Fig. 1) is one of long-acting DHP-derived CCBs (4).

Benidipine is an orally active drug for the treatment of hypertension and angina pectoris synthesized and developed by Kyowa Hakko Kogyo Co., Ltd. Benidipine, approved in Japan in November 1991, has become one of the three best selling CCBs and is highly useful as a potent, long-lasting antihypertensive and antianginal agent. Benidipine is the only DHP-derived CCB satisfying all of the following features: 1) developed in Japan, 2) used once daily, and 3) indicated for angina pectoris, hypertension, and renoparenchymal hypertension. This drug exhibits noteworthy pharmacological actions and fewer side effects.

This review paper outlines the pharmacological characteristics of benidipine.

2. Chemistry

Benidipine is a racemic mixture of two isomers [(*S*)-(*S*)-(+)] and [(*R*)-(*R*)-(-)] (4) in the form of an odorless, yellow crystalline powder. Unlike nifedipine and other related drugs, benidipine is stable under varying light conditions and does not decompose when exposed to high moisture or stored at high relative humidity or in the form of a suspension (5). It is relatively soluble in methanol and ethanol and almost insoluble in water and ether. In the past, gas chromatography (GC) was used to quantify this drug in plasma and other specimens using a Silicon OV-1 column and electron capture detection, allowing it to be detected at a lower limit of 0.3 ng/mL (6). Recently, analytical technology based on liquid chromatography (LC)-mass spectrograph (MS) has allowed the quantitation of benidipine at a lower limit of 0.05 ng/mL (7).

3. Biochemical properties and mechanisms of action

It has been shown electrophysiologically that benidipine inhibits calcium (Ca^{2+}) channels, like other CCBs (8, 9). In addition, this drug has unique biochemical features not seen in other CCBs: 1) Strong, long-lasting action by its high affinity for the DHP binding site and the membrane approach, 2) Renal-protective effects by triple Ca^{2+} -channel blocking, 3) Cardio- and vaso-protective effects by vascular selectivity and enhanced nitric oxide (NO) production.

One characteristic of benidipine is its high affinity for the DHP binding site (i.e., the binding site in Ca^{2+} channels) and cell membranes. The K_i value of benidipine for the DHP binding site is 0.08–0.13 nmol/L, which indicates that this drug has a higher affinity for the DHP binding site than nisoldipine,

nicardipine, nitrendipine, verapamil, and diltiazem (10, 11). In the time course study of the binding of [3 H]-labeled CCBs to rat heart membranes, nitrendipine took 20 min to reach equilibrium, while benidipine took 180 min to reach equilibrium, indicating that the binding of benidipine is very slow (12). In the analysis of the dissociation rate determined by the addition of [3 H]-nitrendipine after the binding of each drug with rat heart membranes, the slope of the dissociation curve was much lower for benidipine than for nifedipine, indicating that dissociation of benidipine takes place very slowly (13). This property of benidipine seems to be associated with its high affinity for cell membranes. The partition coefficient ($\log P_{OW}$) of benidipine, measured by the flask-shaking method, was 3.79. The same parameter measured with LC ($\log P_{HPLC}$) was 4.61, indicating the very high liposolubility of benidipine compared with nifedipine and amlodipine ($\log P_{HPLC}$: 2.20 and 3.95) (14).

In view of the high affinity for cell membranes and the slow binding to and slow dissociation from the DHP binding site, it seems that the concept of the “membrane approach” (approach to the cell membrane followed by long retention in the DHP binding site) is applicable to benidipine (Fig. 2). This concept is generally accepted (15), and the strong and long-lasting activity of benidipine can be clearly explained by this concept.

The second characteristic of benidipine is its inhibitory activity against various subtypes of Ca^{2+} channels. Because nifedipine, the prototype of the DHPs, exclu-

sively blocked muscular L-type Ca^{2+} channels (16), DHPs were considered as selective blockers for L-type Ca^{2+} channels. Over the past several years, studies on Ca^{2+} channels have advanced remarkably, revealing that potential-dependent Ca^{2+} channels can be divided into many subtypes (N, P/Q, R, and T) and clarifying the biochemical properties of each subtype of Ca^{2+} channel (17). It has been reported that benidipine inhibits not only the L-type Ca^{2+} channel, but also especially inhibits the N-type (18) and T-type (19) Ca^{2+} channels. It is estimated that the inhibitory activities of benidipine against various types of Ca^{2+} channel, that is, its triple Ca^{2+} -channel blocking effects, are involved in the pharmacological actions of this drug, such as its reno-protective effects.

The third characteristic of benidipine is vascular selectivity. When the vascular selectivity of various CCBs was evaluated using isolated coronary arteries and the right ventricular papillary muscles of dogs, the coronary artery selectivity of benidipine was 14.4 times higher than that of nifedipine (20) and 19 times higher than that of amlodipine (21). In addition, in vivo receptor binding experiments using spontaneously hypertensive rats indicated that the ratio of binding to peripheral blood vessels to binding to the heart was higher with benidipine than with nifedipine or amlodipine (22). This high vascular selectivity seems to be associated with the pharmacological actions of this drug such as its vasodilative and vaso-protective effects.

Furthermore, in vitro and in vivo basic studies have demonstrated that benidipine has anti-oxidative activity

Fig. 2. Combination of calcium channel blockers with the calcium channel. Usual calcium channel blockers combine directly with the dihydropyridine binding site in the cell membrane, thereby inhibiting the intracellular influx of calcium ions. For benidipine, combination with the binding site is achieved either directly or indirectly, in which a part of benidipine enters the lipid layer of the cell membrane and then diffuses extremely rapidly to the calcium channel protein.

(23), stimulates NO production, suppresses the expression of adhesion molecules (24, 25), stimulates the differentiation of osteoblasts (26), suppresses the proliferation of vascular smooth muscles (27), suppresses the proliferation of mesangial cells, (28), and protects the myocardium (29). The effect of benidipine in stimulating NO production has been clinically endorsed (30). This enhancement of NO production seems to be associated with the pharmacological actions of this drug such as its cardio-protective and anti-atherosclerotic effects.

4. Pharmacokinetics and metabolism

The drug is absorbed rapidly after an oral dose to humans (31), dogs, and rats (32, 33), reaching maximum drug concentration ($C_{\max}$) within 2 h. This short time to maximum concentration after the drug is orally administered ($T_{\max}$) is characteristic of benidipine compared to other CCBs. Table 1 shows the pharmacokinetic parameters after an oral dose of benidipine (2–8 mg) to healthy volunteers (31). The pharmacokinetic parameters of benidipine following repeated oral doses over 7 days (once daily at a dose level of 4 mg) were comparable to those after a single oral dose.

[^{14}C]-Benidipine was transferred rapidly to tissues after an oral administration to rats. Its level was highest in the liver and was also distributed in the kidneys, plasma, and other tissues (32). No tissue showed a particularly high accumulation of the drug following repeated oral administrations to rats (34). Benidipine was highly bound to plasma protein, over 98% in humans, dogs and rats (H. Kobayashi et al., unpublished data).

The percentage urinary excretion of [^{14}C]-benidipine following an oral dose was about 36% in humans (35) and about 20% in rats (36), dogs, and monkeys. Thus, urinary excretion of radioactivity derived from this drug was lower than its fecal excretion, indicating that radioactivity derived from [^{14}C]-benidipine is primarily excreted via bile into feces.

Table 1. Pharmacokinetic parameters of benidipine single dose orally administration in male healthy volunteers

Dose	$T_{\max}$ (hr)	$C_{\max}$ (ng/mL)	AUC (ng · hr/mL)	$T_{1/2}$ (hr)
2 mg	1.1 ± 0.5	0.55 ± 0.41	1.04 ± 1.26	—
4 mg	0.8 ± 0.3	2.25 ± 0.84	3.94 ± 0.96	1.70 ± 0.70
8 mg	0.8 ± 0.3	3.89 ± 1.65	6.70 ± 2.73	0.97 ± 0.34

Data are the mean ± S.D from 6 patients. $T_{1/2}$ means elimination half-life. Reproduced from Y. Uji et al. (31) with permission.

The urinary and plasma levels of unchanged benidipine following an oral dose to rats, dogs, and humans were almost zero (34–37), indicating that the drug is metabolized almost completely. The in vitro experiment on metabolism demonstrated that the drug is primarily metabolized in the liver. No changes in the enzyme activities involved in drug metabolism in the liver were seen in rats after 1 week of oral treatment with the drug, suggesting that this drug does not induce metabolizing enzymes. DHP-derived CCBs are metabolized by the hepatic enzyme cytochrome P450 (CYP). From the inhibitory study of benidipine metabolism in human liver microsomes using CYP isozyme-specific inhibitor and the metabolic study using cell microsomes over-expressed human CYP isozymes, it was assumed that benidipine was mainly metabolized by CYP3A4 (H. Kobayashi et al., unpublished data). When examined in vitro, the inhibition of CYP1A1, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 activities by benidipine was noted at higher concentrations (38), raising concerns about possible drug interactions. However, in view of the results of a study in which benidipine was administered in combination with statins or digoxin in vivo and in vitro, it seems unlikely that benidipine used at ordinary therapeutic dose levels will interact with these concomitant drugs (Y. Sugiyama et al., unpublished data).

In healthy volunteers who orally took benidipine (4 mg) together with 200 mL of grapefruit juice, plasma benidipine levels were higher than those recorded after intake of the drug with water. However, there was no significant difference in plasma drug levels between the benidipine-plus-grapefruit-juice group and the benidipine-plus-water group when determined 1–4 h after the dose. The area under the concentration-time curve was 2.12 times higher compared with the concomitant intake of water, but no difference was noted in blood pressure (H. Kobayashi et al., unpublished data).

In healthy volunteers who orally took benidipine (8 mg) 30 min after a meal, absorption was slower and the plasma levels were higher compared to the parameters recorded after an oral dose of the drug while fasting (Y. Uji et al., unpublished data). These results suggest that it is advisable to take the drug after a meal rather than before a meal.

In hypertensive patients orally treated with 8 mg benidipine, the plasma drug level was almost zero 7 h after the dose, but blood pressure remained reduced and continued till almost 24 h (Fig. 3) (39). These results indicate that benidipine has long-lasting pharmacological activity, proving the concept of the “membrane approach” (40).

Fig. 3. The antihypertensive effect and plasma concentration of benidipine after single oral administration of benidipine hydrochloride (Dose: 8 mg) in patients with essential hypertension. Data are the mean $\pm$ S.E.M. from 6 patients. Reproduced from H. Noda et al. (39) with permission.

5. Toxicity

The toxicity of benidipine was evaluated in mice, rats, guinea pigs, rabbits, and dogs (41–43).

In the acute toxicity study, the 50% lethal dose in rats and mice after a single oral dose ranged from 87.6 to 384.5 mg/kg and was more than 100 times higher than the dose levels exhibiting therapeutic activity such as anti-hypertensive action. In the subacute and chronic toxicity studies, the non-toxic dose level of the drug following 3–12 months of oral treatment was estimated to be 0.38 mg/kg in rats and 0.1 mg/kg in dogs. The major side effects observed in the high-dose groups were fat deposition in the liver, cardiac weight gain, and thymus weight gain, but these side effects tended to subside following cessation of the drug, indicating that they are reversible in nature. No significant problem was observed in the histopathological examination of the heart following treatment with this drug. In the general pharmacological study in mice and rats, treatment with benidipine at high-dose oral treatment (10–30 mg/kg) sometimes resulted in symptoms of suppressed central nervous system activity (e.g., suppressed spontaneous motility), which seemed attributable to an excessive fall in blood pressure.

The drug showed neither carcinogenicity nor anti-genicity. In the reproductive toxicity study using rats and rabbits, the drug showed no teratogenicity. In the mutagenicity study using Chinese hamster lung cells and bacteria, no abnormality was noted. Although some previous reports based on meta-analysis suggest the carcinogenicity of CCBs (44), this possibility has been almost completely rejected.

The results of these studies indicate that benidipine is

highly safe at a wide range of dose levels.

6. Basic pharmacology

6.1. Antihypertensive effects

In the models of hypertension in rats and dogs, benidipine exerted potent, long-lasting antihypertensive activity (45, 46). Based on the “membrane approach” concept unique to benidipine, it was shown that benidipine remained in resistance vessels such as the mesenteric artery even when the plasma drug level had decreased (22). It is thought that persistence of this state contributes to the long-lasting antihypertensive effects of benidipine.

Via a reflex mechanism, most CCBs induce tachycardia and a marked elevation in plasma catecholamines that increase the risk of adverse cardiac events (47). Karasawa et al. demonstrated that benidipine causes relatively less activation of sympathetic nerve activity by hypotensive baroreflex compared to other CCBs (48). In conscious spontaneously hypertensive rats (SHR), oral treatment with benidipine (2 mg/kg) resulted in no significant change in heart rate or plasma norepinephrine level (48). The change in heart rates and plasma norepinephrine levels caused by benidipine was smaller than the changes caused by drugs with comparable antihypertensive activity, that is, nifedipine (5 mg/kg), cilnidipine (6 mg/kg), and amlodipine (3 mg/kg), as shown in Fig. 4. The relatively minor effects of benidipine on sympathetic nerve activity are probably attributable to the following factors: 1) slow expression of antihypertensive action, and 2) inhibition of N- and T-type Ca^{2+} channels involved in the release of catecholamines from sympathetic nerve endings and tachycardia (19). These results indicate that benidipine, which causes less activation of sympathetic nerve activity, can suppress the failure of various organs associated with hypertension, in addition to exerting excellent antihypertensive effects.

In salt-sensitive hypertensive rats, the activity of the renin-angiotensin system (RAS) is low, and the antihypertensive effects of RAS inhibitors [angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs)] have been shown to be weak in these rats (49). Benidipine exerted excellent antihypertensive effects in a RAS-independent manner (46, 50–52). These results suggest that benidipine is highly effective against salt-sensitive hypertension, which is difficult to treat with RAS inhibitors. Furthermore, benidipine has been shown to exert natriuretic activity at dose levels exhibiting antihypertensive effects (46, 53), suggesting that this activity contributes to the antihypertensive effects of benidipine.

Fig. 4. Comparative illustration of the effects of benidipine, nifedipine, cilnidipine and amlodipine on blood pressure and heart rate in conscious spontaneously hypertensive rats. Delta systolic blood pressure (sBP) and delta heart rate (HR) represent the area under curve (AUC) for the changes in sBP and HR, respectively, from 0 to 10 h after the drug administration. Each column represents the mean $\pm$ S.E.M. of 6 animals. * $P < 0.05$, ** $P < 0.01$, # $P < 0.001$: significant differences compared with the value for benidipine (Dunnett test following ANOVA). Reproduced from A. Karasawa et al. (48) with permission.

Fig. 5. Effects of candesartan (1 mg/kg; C), benidipine (4 mg/kg; B), amlodipine (4 mg/kg; A), and candesartan combined with benidipine (C + B) or amlodipine (C + A) on systolic blood pressure and urinary albumin excretion in Dahl salt sensitive hypertensive rats. Drugs were orally administered once a day for 4 weeks. Each point represents the mean $\pm$ S.E.M. of 7 or 8 rats. * $P < 0.05$, ** $P < 0.01$: significant differences compared with the value in the control group. ††† $P < 0.001$: significant differences compared with the value in the C group (Wilcoxon's rank sum test). Modified from K. Yao et al. (54) with permission.

Recently, combination therapy with different types of antihypertensive drugs has been increasingly used to improve the clinical benefits of monotherapy. Benidipine exerts excellent antihypertensive and organ-protective effects when used in combination with RAS inhibitors (50, 52, 54). In addition, the combination of candesartan, an ARB, and benidipine reduces blood pressure and inhibits renal dysfunction more effectively than the combination of candesartan and amlodipine (54, Fig. 5).

It is thus suggested that benidipine exerts reliable anti-hypertensive, organ-protective effects if used in combination with RAS inhibitors when adequate anti-hypertensive effects are not achieved by RAS inhibitors alone.

6.2. Renoprotective effects

Uncontrolled hypertension has been related to increased cardiovascular morbidity and progressive renal functional impairment (55). The kidney plays an impor-

Fig. 6. Effects of benidipine, amlodipine, and nifedipine on angiotensin II-induced constriction of renal microvessels. Both amlodipine and nifedipine reversed the afferent arteriolar constriction. In contrast, benidipine elicited dilation of efferent as well as afferent arterioles. * $P < 0.05$ vs. afferent arterioles. Modified from K. Hayashi et al. (56) with permission.

tant role in the regulation of circulation. Renal damage can disturb the regulation of bodily fluid associated with abnormal sodium metabolism, leading to exacerbation of hypertension and further deterioration of renal function (a vicious cycle). Therefore, suppressing the onset or progression of renal damage is important, not only for blood pressure control in cases of hypertension but also for prevention of hypertension-induced disorders of other organs (56).

Previous studies demonstrate that glomerular hypertension is an important factor in the mechanism for the onset of hypertensive glomerular injury (57). Blood filtration, which is a major function of the kidneys, is performed by glomeruli. Regulation of the resistance of afferent and efferent arterioles, located before and after the glomeruli, allows sensitive regulation of glomerular filtration. The L-type Ca^{2+} channel, which is the site of action of CCBs, predominates at the afferent arteriole, and traditional CCBs preferentially dilate afferent arterioles rather than efferent arterioles (56, 58, 59). The dilation of afferent arterioles might induce elevation in intraglomerular pressure, leading to glomerular hypertension. Several studies have shown that benidipine dilates both the afferent and efferent arterioles (56, 60–63). In a study using rats with hydronephrosis, the microcirculation of isolated kidneys was directly observed with a charge coupled device camera to evaluate the effect of benidipine in dilating the afferent and efferent arterioles of the kidneys (56). In that study, nifedipine was found to primarily dilate the afferent arterioles, while benidipine dilated not only the afferent arterioles but also the efferent arterioles (Fig. 6). Furthermore, in vivo micropuncture studies have revealed that benidipine reduces glomerular pressure in SHR (60). In anesthetized dogs, benidipine dilated both the afferent and the efferent arterioles, but amlodipine

preferentially dilated the afferent arteriole (61). The effect of benidipine in dilating efferent arterioles can be explained by a mechanism other than suppression of the L-type Ca^{2+} channel. In particular, suppression of the T-type Ca^{2+} channel involved in the dilation of efferent arterioles seems to be closely related to this effect.

Consequently, it is thought that benidipine does not cause elevation in glomerular pressure, as benidipine dilates both afferent and efferent arterioles. Many DHP-derived CCBs preferentially dilate afferent arterioles. The effect of dilating efferent arterioles seems to be characteristic of benidipine and probably contributes to the beneficial renoprotective effects of this drug.

Benidipine also exerts natriuretic effects at dose levels exhibiting antihypertensive effects (46, 53, 63). The diuretic effect of benidipine is more potent than that of amlodipine, and this seems to be partially attributable to its effect of increasing renal blood flow (63). When benidipine was administered to SHR, the lithium (Li) clearance in the kidneys was elevated, without affecting the glomerular filtration rate, indicating that this drug inhibits the reabsorption of water and sodium at the proximal tubule (53). On the other hand, stop-flow experiments indicated that benidipine suppressed sodium reabsorption at the distal tubules as well (53). Thus, benidipine seems to exert natriuretic effects by acting on both the upper segment of tubules and the distal tubules.

In acute and chronic renal failure models in rats, benidipine suppressed renal tissue damage and renal dysfunction (64–67). In rats with acute ischemic renal failure, intravenous treatment with benidipine ($10 \mu\text{g}/\text{kg}$) suppressed elevation in serum creatinine and blood urea nitrogen, the reduction in renal ATP, the elevation in lipid peroxide, and the elevation in intracellular calcium levels following reperfusion (64). These effects of benidipine were more potent than those of other DHP-

derived CCBs such as nifedipine, nitrendipine, and amlodipine (64, 65). Histopathologically, benidipine suppressed both the necrosis and apoptosis of tubules (65). In SHR with 5/6 nephrectomy (a model of chronic renal failure) and stroke-prone spontaneously hypertensive rats (SHRSP), benidipine suppressed the progression of renal dysfunction (67, 68). In Dahl salt-sensitive hypertensive rats, benidipine suppressed the progression of albuminuria and sclerotic changes in the glomeruli (50–52, 54), and these effects of benidipine were more potent than those of amlodipine, known to exert a similar degree of anti-hypertensive activity (54, Fig. 5).

Regarding the effects of benidipine on glomerular nephritis, it has been reported that benidipine suppressed the increase in urinary protein excretion and the proliferation of mesangial cells (69). Benidipine also suppressed the increased expression of transforming growth factor (TGF)- β and α -smooth muscle actin in the glomeruli. Since hydralazine did not prevent progression to nephropathy, these effects are not attributable simply to the anti-hypertensive effects of the drugs. When Dahl salt-sensitive rats and SHRSP were treated with benidipine, glomerular platelet-derived growth factor (PDGF) β -receptor tyrosine phosphorylation was suppressed, and nephroprotective effects were observed (68). These results suggest that the effect of benidipine in suppressing factors other than glomerular pressure (e.g., TGF- β and PDGF) is also associated with its renoprotective effects. Thus, benidipine seems to be capable of correcting glomerular pressure better than other DHP-derived drugs and to serve as a beneficial CCB with renoprotective effects.

6.3. Vascular endothelial protective effects

One of the distinguishing characteristics of benidipine is its effect in protecting the vascular endothelium. Vascular endothelial cells line the inner vascular wall and play diverse physiological roles such as vascular relaxation and contraction, thrombogenesis, fibrinolysis, and platelet activation (70). Damage to or dysfunction of the endothelium can trigger cardiovascular diseases (e.g., progression of atherosclerosis and thrombus formation) and is probably involved in the onset of hypertension and ischemic heart disease. In experimental models of endothelial cell damage associated with hypertension (52, 71), ischemia-reperfusion injury (72, 73), and challenge with toxic chemicals such as sodium citrate (74) or vitamin D₂ plus nicotine (75), benidipine prevented endothelial dysfunction. It has been suggested that most vascular endothelial cells do not express L-type Ca²⁺ channels (76, 77). Benidipine seems to protect the endothelium through mechanisms

other than the inhibition of Ca²⁺ channels.

In a recent study using cultured endothelial cells, benidipine suppressed endothelial damage induced by lysophosphatidylcholine [one of the lipids constituting oxidized low density lipoprotein (LDL)] more potently than nifedipine and amlodipine (78). One possible mechanism for this effect of benidipine is the suppression of the formation of oxygen radicals. Since oxidized LDL is a factor responsible for the onset and progression of atherosclerosis, this finding suggests that benidipine may suppress the onset of atherosclerosis. In the model of intimal thickening in the carotid artery of mice, benidipine elevated the endothelial nitric oxide synthase (eNOS) levels in vascular endothelial cells, and the increased NO improved vascular remodeling despite the lower reduction of blood pressure (79). Some investigators reported that NO suppresses damage to the endothelial cells induced by oxidized LDL in addition to exerting direct protective effects on the cells that constitute the vascular wall (80). Therefore, benidipine is expected to suppress the progression of atherosclerosis by stimulating the formation of NO by its direct action on vascular endothelial cells in addition to exerting anti-oxidative effects.

Moreover, in a rat subjected to balloon catheter-induced endothelial denudation of the aorta, intimal thickening was suppressed by benidipine (5 mg/kg, p.o., b.i.d.) (27, 81). This effect was not exerted by nifedipine (10 and 20 mg/kg, p.o., b.i.d.). These results suggest that benidipine may additionally prevent the onset of atherosclerosis associated with endothelial damage.

6.4. Cardioprotective effects

In many experimental models of ischemic heart disease in vitro and in vivo, the effect of benidipine in protecting the myocardium was demonstrated (73, 82–91). Recently, studies to elucidate the mechanism for these cardioprotective effects of benidipine have advanced. These results suggest that the cardioprotective effects of benidipine involve not only a marked increase in coronary blood flow and the suppression of calcium overload, but also anti-oxidative and vascular endothelium-protective activities. These effects of benidipine seem to appear at dose levels lower than those required by nifedipine, due to the “membrane approach” (91, 92). Benidipine more powerfully suppresses the anoxic contraction of isolated coronary arteries compared to nifedipine (92). These results suggest that in the presence of ischemia (e.g., that prevails in patients with angina pectoris), benidipine can more effectively suppress coronary artery contraction.

In anesthetized dogs, benidipine (100 ng/kg/min) elevated coronary blood flow through the ischemic

myocardium, alleviated the reduction in myocardial contractility, and reduced metabolic disorders (84). These effects of benidipine were suppressed by *N*-nitro-L-arginine-methyl ester (L-NAME), an NO synthetase inhibitor, suggesting that the NO-increasing effect is involved in the effect of benidipine in increasing coronary blood flow. Benidipine was also reported to limit infarct size via a bradykinin- and NO-dependent mechanism in dog hearts (85). Reperfusion of the ischemic myocardium can lead to the massive production of free radicals. These free radicals have been considered as a highly probable factor responsible for post-ischemic reperfusion injury (93). When myocardial interstitial hydroxyl radicals during ischemia and reperfusion in rabbits were measured using microdialysis, it was found that benidipine significantly suppressed the formation of hydroxyl radicals following reperfusion (89). This led to a significant decrease in the size of the infarcted area. The infarct-reducing effect of benidipine in this model was suppressed by chelerythrine (a protein kinase inhibitor) and L-NAME. These results suggest that the myocardium-protective effect of benidipine following reperfusion involves the suppression of free radical formation through the activation of protein kinase C and increased NO formation.

Intravenous treatment with benidipine (3 and 10 μ g/kg) suppressed not only myocardial necrosis associated with reperfusion after coronary artery ligation but also apoptosis following reperfusion (86, 87). These findings suggest that the inhibitory effect on apoptosis contributes to cardiac protection. Recent reports suggest the involvement of apoptosis in myocardial damage associated with hypertension, ischemic heart disease, and heart failure (94). Benidipine is expected to exert cardioprotective effects in these diseases. However, further studies are needed to fully clarify the relationship between apoptosis and cardiac disease.

Benidipine at dose levels exerting little effect on blood pressure suppressed the progression of myocarditis in mice, accompanied by marked suppression of the expression of myocardial interleukin-beta and inducible nitric oxide synthase (iNOS) (95). These results suggest that benidipine increases NO formation associated with eNOS but does not increase NO formation associated with inflammatory iNOS.

Potent antianginal effects of benidipine have been shown in various models of angina (90, 91, 96). Combination effects of benidipine and diltiazem for the treatment of angina have also been reported in rats (90). Benidipine shows more vascular selectivity and less negative inotropic activity compared to diltiazem, and induces a longer-lasting increase in coronary blood flow (96, 97). Diltiazem also increases coronary blood flow,

but this effect is transient, unlike the similar effect of benidipine (97). Diltiazem has a beneficial effect in reducing myocardial oxygen consumption by reducing heart rate, and this effect contributes to its antianginal effects. Combination therapy of benidipine and diltiazem might possess favorable properties as a treatment for angina pectoris because benidipine has more potent coronary vasodilating activity than diltiazem, and diltiazem reduces myocardial oxygen demand more effectively than benidipine.

Benidipine suppressed cardiac hypertrophy in hypertensive rats and improved microvascular remodeling in these rats (50, 51, 98 – 101). In rats with renovascular hypertension, treatment with benidipine resulted in a reduction in cardiac hypertrophy and an increase in left ventricular NO formation and eNOS mRNA levels (99). The reduction in capillary density and the thickening of the vascular wall seen in this rat model were suppressed by benidipine (99). According to a recent report, benidipine inhibits myocardial remodeling induced by chronic NO inhibition, by inhibiting both the 70-kDa ribosomal protein S6 kinase and the extracellular signal-regulated kinase in rats (101). These effects, in addition to lowering blood pressure, may be attributable to the cardioprotection provided by benidipine.

6.5. Other effects

Like other CCBs, benidipine increases cerebral blood flow, and this effect of benidipine lasts longer than that of nifedipine (96). In SHR, benidipine suppressed dysfunction and morphological changes in the basilar artery (102). In rats with acute ischemic injury of the brain, benidipine exerted brain-protective effects (103). In salt-loaded SHRSP, the suppression of cerebrovascular lesions by benidipine was demonstrated in a study using magnetic resonance imaging (104). Benidipine has been shown to induce an increase in cerebral blood flow and a decrease in the lower limit of the autoregulation of cerebral blood flow (J. Ikeda et al., unpublished data). Benidipine is thus promising as a means of treating hypertension complicated by cerebrovascular disease.

Insulin resistance can lead to compensatory hyperinsulinemia, which can induce hypertension through various mechanisms. In fructose-loaded hypertensive animals with insulin resistance, benidipine exerted anti-hypertensive effects and reduced insulin resistance (105). In Otsuka Long-Evans Tokushima fatty rats (a model of type II diabetes mellitus), benidipine suppressed cardiac remodeling, probably through a mechanism involving the suppression of vascular expression of TGF- β , vascular endothelial growth factor, and basic fibroblast growth factor (106). Benidipine additionally

suppressed the progression of diabetic nephropathy (106). In view of these findings on the effects of benidipine in reducing insulin resistance and protecting organs from injury due to diabetes mellitus, it seems likely that benidipine is also useful in the treatment of hypertension complicated by diabetes mellitus.

It has been reported that benidipine has unique effects on bone (26, 107–109). Oral treatment of SHR with benidipine (3 mg/kg per day) for 8 weeks resulted in increased femoral bone strength and tibial bone mineral content (109). In cultured osteoblasts, benidipine elevated alkaline phosphatase activity at dose levels over 1 pmol/L, suggesting that benidipine stimulates the differentiation of osteoblasts (26). About 10,000 times higher concentrations of amlodipine or nifedipine were needed for these drugs to exert effects comparable to the above-mentioned effects of benidipine. These results suggest that benidipine exerts beneficial effects on bone at dose levels close to those needed for the expression of antihypertensive effects.

7. Clinical pharmacology

7.1. Hypertension

In a late phase II study on the antihypertensive effects of benidipine, 110 patients with mild or moderate essential hypertension were treated. Their response rate (the percentage of patients showing a reduction in blood pressure) was 86.4%, and the incidence of side effects was 5.9% (110). When the effects of benidipine used in combination with diuretics or beta-blocking agents were evaluated in the same clinical study, the response rate was 90.9% ($n = 55$), and the incidence of side effects was 5.0% (110). When benidipine was combined with beta-blockers, the response rate was 87.5% ($n = 32$), and the incidence of side effects was 7.9% (110). When the effects of benidipine in 36 patients with severe hypertension were evaluated, high efficacy and safety were noted, with the response rate of 94.4% and side effect incidence of 5.4% (111). No significant change in heart rate was observed in any of these clinical studies.

The guidelines for the management of hypertension (JSH2004) edited by Japanese Society of Hypertension have been published, setting the target of anti-hypertensive therapy at reducing blood levels to less than 140/90 mmHg (112). Anan et al. compared the degree of achieving this target in two groups of patients: 1) a group treated with benidipine at a dose level of 4 mg/day (increased to 8 mg/day if response was inadequate) ($n = 15$) and 2) a group of patients treated with amlodipine at a dose level of 2.5 mg/day (increased to 5 mg/day if response was inadequate) ($n = 14$) (113). In that study, the percentage of cases achieving the target of

blood pressure after 8 weeks of treatment was 66.7% in the benidipine group and 35.7% in the amlodipine group. These results suggest that benidipine exerts potent anti-hypertensive effects even when used independently. The anti-hypertensive effect of benidipine on the basis of analysis of circadian variation in blood pressure has also been evaluated using ambulatory blood pressure monitoring (114). Once daily treatment with benidipine showed reliable anti-hypertensive effects compared to the placebo group, without significantly changing the heart rate.

The T/P ratio, an indicator of the duration of anti-hypertensive activity, has also been studied (115). In a placebo-controlled double-blind crossover study, the T/P ratios as calculated from systolic and diastolic blood pressures were 82 and 64, respectively, thus satisfying the WHO-recommended T/P ratio (over 50). These results are comparable or superior to the results for other long-lasting CCBs.

As stated above, benidipine was clinically shown to serve as a CCB with reliable, long-lasting anti-hypertensive activity based on the “membrane approach.”

The JSH2004 Guidelines recommend restricting salt intake to stay below 6 g/day, because Japanese people tend to consume too much salt (112). A crossover study of benidipine and nifedipine was carried out in 25 salt-sensitive hypertensive patients to evaluate the effects of salt loading on blood pressure, organ blood flow (measured by Doppler ultrasonography), and so forth (116). In this study, the reduction in blood pressure following benidipine treatment was not changed by salt loading, while blood pressure rose in the patients treated with nifedipine under salt loading. Renal blood flow was maintained in the benidipine treatment group with or without salt loading, while it was significantly decreased in the nifedipine treatment group loaded with salt, as shown in Fig. 7.

The incidence of cerebral, cardiac, and vascular events was analyzed in 354 elderly patients with hypertension treated with benidipine for 2 years (117). In these patients, with a mean age of 71.3 years, the mean blood pressure decreased from 173/95 to 142/80 mmHg after 2 years of benidipine treatment. The annual incidence of stroke was 3.5 per 1,000 patients, and the annual incidence of cardiovascular events was 5.3 per 1,000 patients. Exact comparison of this study with other studies is difficult because patient background and the number of patients were different, but the incidence of these events was suppressed by benidipine to a degree superior to that obtained in the other studies if we take the age of the patients into account (118–120).

Fig. 7. Changes in hemodynamic indexes with sodium repletion in the absence (run-in) and presence of calcium antagonists (benidipine, nifedipine) in the salt-sensitive patients ($n = 15$). Sup Mes Flow, superior mesenteric flow; T-Ao Flow, terminal aortic flow; L, low sodium diet (open bars); H, high sodium diet (hatched bars). Data are expressed as mean $\pm$ S.D. * $P < 0.05$, ** $P < 0.01$, statistical significance of differences between low and high sodium diets. Reproduced from H. Shimamoto et al. (116) with permission.

7.2. Prevention of the progression of renoparenchymal hypertension and nephropathy

Forty-one patients definitely diagnosed as having renoparenchymal hypertension were treated either with benidipine alone (2–8 mg/day) or with benidipine plus diuretics (121). The response rate after 8 weeks of treatment was 82.4%, and the incidence of side effects was 5.1%. On the basis of these results, the indications for benidipine were expanded in June 1994 to include renoparenchymal hypertension.

Fifteen patients with hypertension complicated by type II diabetes mellitus were treated with benidipine (4–8 mg/day) for 3 years, and the time courses of anti-hypertensive effects and the renal function were measured (122). The patients studied were in the early stages of nephropathy, with urinary microalbumin excretion between 30 and 300 mg/g $\cdot$ Cr. When the course of these 15 patients was compared to the untreated control group with matched background variables for a period of 3 years, the mean blood pressure in the benidipine group was decreased significantly from the baseline 110 to 98 mmHg after 3 years of the treatment, while the control group showed no significant reduction in blood pressure. When the time course of urinary albumin excretion was measured, the urinary albumin level in the control group was gradually increased, reaching a level

Fig. 8. Changes in urinary albumin during the 3-year follow-up in type 2 diabetic patients treated with benidipine (BE) or non-benidipine (DM). Data are expressed as mean $\pm$ S.E.M. Significantly less albuminuria occurred in the benidipine group ($P < 0.05$) compared with the non-benidipine group over 12–36 month (except 18 month). Reproduced from T. Noguchi et al. (122) with permission.

significantly higher than the level in the benidipine treatment group (Fig. 8). This study suggests that benidipine may suppress the progression of nephropathy during the subsequent 3-year period.

Ishimitu et al. administered benidipine or enalapril (an ACE inhibitor) to 22 patients with hypertension and

diabetes mellitus for 3 years and measured the time courses of blood pressure, fasting blood glucose, hemoglobin A1c (HbA1c), urinary albumin, and serum creatinine levels (123). When blood pressure response was insufficient, diuretics were added to benidipine or enalapril (1 case in the benidipine group and 4 in the enalapril group). The benidipine treatment group tended to show a better blood pressure response. Urinary albumin excretion tended to be decreased more greatly, but not significantly, in the benidipine group than in the enalapril group. The time course of the serum creatinine level indicates significantly more suppression of renal damage in the benidipine group. This result may reflect the better control of blood pressure in the benidipine group. These results suggest that, as observed in the VALUE study (124), the control of blood pressure is the best therapy for diabetic hypertensive patients and that there are some organ-protective effects of benidipine as well as RAS inhibitors in diabetic patients in addition to the anti-hypertensive effects.

A prospective randomized comparison between benidipine and nifedipine for 3 years has recently been reported (125). The time course of blood pressure was similar in both the benidipine treatment group and the nifedipine treatment group. The percentage of patients who reached the primary endpoint (a 1.5-fold rise in the serum creatinine level from the baseline, requiring hemodialysis or kidney transplantation, eventually leading to death) was significantly lower in the benidipine treatment group than in the nifedipine treatment group (Fig. 9).

These clinical studies revealed that benidipine suppresses the progression of nephropathy, and this renal-protective effect may be attributable to the following mechanisms: 1) reduction in glomerular pressure

after dilation of the efferent arterioles due to inhibition of T-type Ca^{2+} channels, 2) marked increase in renal plasma flow rate, 3) natriuretic effect, and 4) increased NO formation in the renal parenchyma.

7.3. Angina pectoris

A phase III study, a double-blind clinical trial comparing benidipine with nifedipine, was conducted on 127 patients with angina pectoris (126). The frequency of anginal attacks and of sublingual nitrate dose tended to be lower in the benidipine treatment group than in the nifedipine treatment group. In the evaluation of usefulness, benidipine was rated as the first CCB superior in efficacy to nifedipine. All of the CCBs, approved and marketed for use in the treatment of angina pectoris after the report of this study, had efficacy comparable to that of nifedipine.

The cohort study reported recently by the Department of Cardiology, Kyushu University, endorsed results obtained in phase III studies (127). A cohort study involving 726 patients undergoing vasospastic angina (VSA) treatment was conducted from 1981 to 2002. During this study, various background variables were measured, and the effects of nitrates, beta-blockers, and many CCBs, and so forth, on prognosis were evaluated. Among these drugs, only benidipine exerted a better prognostic effect in the therapy for patients with VSA (Fig. 10 and Table 2).

Although DHP-derived CCBs have been generally developed as drugs for the treatment of vasospastic angina pectoris, benidipine has also been shown to be effective against effort angina (128, 129). This effect is probably explained by the results of the cardiohemodynamics during exercise in patients with effort angina, that benidipine, unlike nifedipine and some other drugs,

Fig. 9. Renal survival in hypertensive patients with renal impairment administered (—) benidipine or (---) nifedipine retard. * $P < 0.05$ (log-rank test: $P = 0.014$, Wilcoxon's test: $P = 0.022$), $n = 15$ for each of the benidipine- and nifedipine-treated groups. Modified from S. Inoue et al. (125).

Fig. 10. Effect of benidipine on survival without cardiovascular events in patients with vasospastic angina. Reproduced from A. Ito et al. (127) with permission.

Table 2. Effect of medical treatment on the survival without cardiovascular events of patients with vasospastic angina before and after 1990

Drugs	Before 1990 (n = 138)				After 1990 (n = 527)			
	Odds	95% CI		P Value	Odds	95% CI		P Value
		Lower	Upper			Lower	Upper	
Ca blockers	1.053	0.122	9.099	NS	—	—	—	—
Diltiazem	1.349	0.450	4.046	NS	1.318	0.601	2.894	NS
Nifedipine	1.014	0.335	3.066	NS	2.280	0.935	5.561	NS
Benidipine	—	—	—	—	0.281	0.084	0.943	0.0398
Amlodipine	—	—	—	—	0.771	0.287	2.068	NS
Nitrates	1.071	0.355	3.229	NS	2.551	1.021	6.377	0.0451
Nicorandil	2.375	0.441	12.790	NS	1.468	0.578	3.726	NS
β -blockers	5.429	1.364	21.614	0.0164	1.905	0.816	4.446	NS

Ca blockers, calcium channel blockers; NS, not significant. Reproduced from A. Ito et al. (127) with permission.

decreases blood pressure without causing a rise in heart rate, leading to a reduction in pressure rate product. Furthermore, as shown in basic studies, benidipine enhances NO production during ischemia, leading to increased coronary blood flow (33, 34). These effects of benidipine probably protect the myocardium, contributing to better prognosis for angina pectoris.

7.4. Others

7.4.1. Effects on insulin sensitivity

In 25 non-obese patients with essential hypertension without diabetes mellitus, benidipine or placebo was administered for 12 weeks (130). Insulin sensitivity was measured using the steady state plasma glucose (SSPG) method. SSPG level was significantly higher in hypertensive patients, indicating insulin resistance, and benidipine ameliorated insulin resistance (Fig. 11). Moreover, benidipine significantly decreased blood pressure, but did not affect blood norepinephrine levels in this study. It is known that quick-acting nifedipine often stimulates sympathetic nerve activity in a reflexive manner and affects catecholamines such as norepinephrine. Benidipine, on the other hand, did not affect catecholamines, thus allowing a reduction in insulin resistance, as well as a decrease in blood pressure. When 23 patients with hypertension complicated by diabetes mellitus were treated with benidipine for 6 months, adequate anti-hypertensive effects were observed without influence on fasting blood glucose levels or blood glucose levels after a 75 g oral glucose tolerance test (131).

In pancreatic beta cells, it is known that ATP opens the voltage-dependent Ca^{2+} channel via closing the K^{+} channel, leading to calcium influx and secretion of insulin. Therefore, CCBs may inhibit insulin secretion. However, the above results suggest that benidipine

Fig. 11. Effects of treatment (12 weeks) with benidipine and placebo administration on insulin sensitivity to glucose utilization in patients with essential hypertension (the benidipine group, n = 11; the placebo group, n = 14). Open bar, before treatment; hatched bar, after treatment. * $P < 0.05$ vs. normal control subjects; § $P < 0.05$, between groups. Values are means $\pm$ S.E.M. (): number of subjects. Modified from M. Suzuki et al. (130).

does not affect insulin secretion.

7.4.2. Effects on lipid metabolism

Seventeen hypertensive patients with non-insulin dependent diabetes mellitus were treated with benidipine for 6 months, and the time courses of blood neutral fat, high density lipoprotein (HDL)-cholesterol, and LDL-cholesterol levels were followed (132). Blood triglyceride level was decreased significantly after the benidipine treatment, but LDL-cholesterol was unchanged. Blood HDL-cholesterol level began to show a significant increase 3 months after the benidipine treatment. Yamakado et al. also studied the effects of benidipine on serum lipids and apoproteins in 14 patients with essential hypertension treated for one year (133). Benidipine did not affect serum lipids, but

decreased triglyceride levels significantly, accompanied by significant reduction in apo C-II, C-III, and E. Furthermore, serum oxygen radical scavenger activity (like superoxide dismutase activity) was significantly increased, whereas serum lipid peroxide levels was significantly decreased.

These results indicate that benidipine may improve lipid metabolism in addition to the anti-hypertensive effect. It is also noteworthy that the anti-oxidative activity of benidipine was observed in clinical studies as well as basic experiments.

7.4.3. Effects on uric acid metabolism

In general, ACE inhibitors, ARB, and CCBs have little effect on blood uric acid level. Ten patients with essential hypertension were treated with benidipine for 1 month, and blood levels of uric acid, lactic acid, ammonia, and hypoxanthine were measured before and after a semi-ischemic forearm exercise test (134). Serum uric acid level ($34.3 \pm 23.4 \rightarrow 25.2 \pm 21.2$ mg/dL) decreased significantly, and ammonia ($104 \pm 154 \rightarrow 38 \pm 71$ μ g/dL) and hypoxanthine ($1.98 \pm 2.2 \rightarrow 0.69 \pm 0.76$ μ g/mL) levels also decreased significantly. When a similar study was conducted on manidipine, the formation of ammonia and hypoxanthine was not suppressed. Therefore, the mechanism by which benidipine reduces uric acid levels probably involves a pleiotropic effect, not a Ca^{2+} -channel blocking effect. In other words, it seems likely that benidipine alleviates myogenic hyperuricemia observed in hypertensive patients by 1) stimulating renal excretion of uric acid and 2) suppressing the formation of hypoxanthine in skeletal muscles.

8. Safety and side effects

During the clinical study of benidipine conducted in Japan from November 1991 (immediately after the launch of this drug) to October 1997, 4,679 patients were examined. In total, 361 side effects or laboratory abnormalities were seen in 219 patients (4.7%). The major side effects were palpitation (24 cases, 0.5%), hot flushes (22 cases, 0.5%), and headache (20 cases, 0.4%), which are often seen in other CCBs.

These major side effects seem to be attributable to the vasodilative activity immediately after the administration, so that the severity of the side effects caused by the CCBs is related to T_{max} (135). Benidipine, different from other CCBs, has a short T_{max} (0.8–1.1 h) with few side effects. This is because benidipine acts slowly on the DHP binding site through the mechanism called the “membrane approach.”

9. Conclusion

Benidipine is a DHP-derived CCB developed in Japan. It is a drug with several unique mechanisms of action, that is, triple Ca^{2+} -channel blocking action with a membrane approach. Benidipine has relatively high vascular selectivity among DHP-derived CCBs and is expected to show the protective effects on vascular endothelial cells. Renal protective effects of benidipine, particularly characteristic, also have been shown in several basic and clinical studies. Moreover, anti-oxidative action and enhancing NO production have been noted with this drug, following the cardio-protective effects in patients with ischemic heart disease. In fact, benidipine exerted a better prognostic effect than other CCBs in the therapy for patients with VSA. Clinically, combination therapy is expected to play a central role in the treatment of hypertension now and in future, and CCBs are often used in combination with ARB in the therapy for hypertensive patients. In basic studies, treatment with a combination of benidipine and ARB yielded better results than amlodipine plus ARB treatment. Therefore, benidipine is a CCB expected to be useful in combination therapy for hypertension.

Benidipine was launched on the Japanese market 14 years ago, but few severe side effects have been reported, suggesting that this is a drug with established safety. Benidipine is now available in several Asian countries (e.g., China, Korea, and the Philippines).

Acknowledgments

We express sincere thanks to Drs. Hiroyuki Kobayashi and Kenji Ohmori (both belonging to Pharmaceutical Research Center, Kyowa Hakko Kogyo Co., Ltd.) for their helpful advice and suggestions.

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