[연수강좌]

칼슘 길항제(Efonidipine)

이 홍 수

이대목동병원 가정의학과

Calcium antagonists(CA)

- 1980년대부터 혈압강하제로 사용
- 1차 치료 약 중의 하나
- 고혈압 환자의 1/3 – 1/4 사용
  - 효과적인 강압; 년령, 종족, 염분섭취에 무관
  - Metabolic neutrality; 혈당, 지질
  - 부작용이 적다; 두통, 홍조, 부종
  - 심장과 신장 등 표적장기의 보호효과

Evolution of Ca Antagonists

First Generation : conventional
-- verapamil, diltiazem, nifedipine,

⇓

Second Generation : modified release
-- felodipine isradipine, nicardipine, nitrendipine
-- verapamil SR, nifedipine XL, felodipine ER,
diltiazem CD, isradipine CR

⇓

Third Generation : intrinsically long-acting

1. Long plasma half life	2. Long-receptor half life
Amlodipine	Lercanidipine, Lacidipine Cilnidipine, Efonidipine

1세대: mulitiple dosing due to their **short half-life.**
2세대: once-a-day agents characterized by a **delayed or modified release mechanism.**
3세대: inherently long-acting agents, The **long-receptor half-life agents.** characteristically have a great degree of lipophilicity

고혈압 치료에 이용되는 CA 분류

조직 선택성	제 1 세대	제 2 세대		제 3 세대
		Novel formulations (IIa)	New chemical entities (IIb)	
Dihydropyridine (artery > cardiac)	Nifedipine Nicardipine	Nifedipine SR/GITS Felodipine ER Nicardipine SR	Benidipine Isradipine Manidipine Milvadipine Nimodipine Nisodipine Nitrendipine	Amlodipine Lacidipine Lercanidipine Cilnidipine **Efonidipine**
Benzothiazepine (artery = cardiac)	Diltiazem	Diltiazem SR		
Phenylakalamine (artery≤cardiac)	Verapamil	Verapamil SR	Gallopamil	
Phenylakalamine /Benzimidazolyl (artery>cardiac)	Mibefradil			

Classification of Ca Channel

		저 전위 활성형	고 전위 활성형		
		T type	L type	N type	P type
제 1세대	Nifedipine	–	++	–	–
	Verapamil	–	+	–	–
	Mibefradil	+	–	–	–
제 2세대	Manidipine	–	++	–	–
	Nilvadipine	–	+++	–	–
	Barnidipine	–	++	–	–
	Benidipine	–	++	–	–
제 3세대	Amlodipine	–	+	+	–
	Cilnidipine	–	++	++	
	Lacidipine	–	++	–	–
	Lercarnidipine	–	++	–	–
	Efonidipine	++	++	–	–
존재부위		중추/ 말초신경, **혈관 평활근,** SA node, Purkinje fibers	중추/ 말초신경, **심근, 혈관 평활근** 골격근,	중추, 말초신경	중추, 말초 신경

New classification of Ca antagonists(TARGET-BASED)

Classification	약 제	혈관 확장	Effect on heart		Disease
			수축력	심박수	
Non-selective L-type CCB	Diltiazem Verapamil	+	↓	↓	Hypertension Angina pectoris
Vasoselective L-type CCB	Nifedipine	++	→	↑ ~ →	Hypertension
L- & N-type CCB	Cilnidipine	++	→	→ ~ ↓ N-type Ca channel	Hypertension (Angina pectoris) Decrease in sympathetic activity
L- & T-type dual CCB	Efonidipine	++	→	↓ T-type Ca channel	Hypertension Angina pectoris Organ protection (Cardiac & Renal protection)

Product Information

1. Component : Efonidipine HCl (3rd Dihydropyridines Ca^{2+} channel antagonist)
2. Reimbursement Price : 471/T,314/T (40mg, 20mg Round coated tablet)
3. Mechanism
   a. L-Type Ca channel Blocking : Vasodilation
   b. T-Type Ca channel Blocking : Decrease in High Heart rate

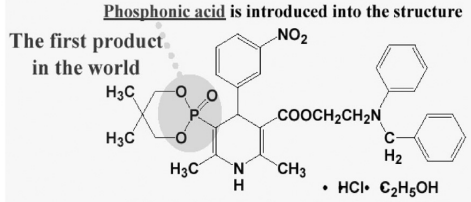
Product Information

5. Indication : Essential Hypertension, Angina pectoris, Renal Hypertension
6. Features
   a. Sustained anti-hypertensive effect
   b. Good efficacy on Angina pectoris
   c. Decrease high heart rate
   d. Renal protection
   e. CV protection effect in hypertension with DM

Chemistry

Phosphonic acid is introduced into the structure

The first product in the world

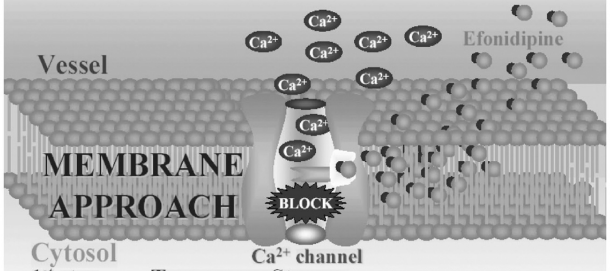


Efonidipine hydrochloride (FINTE)

Nifedipine

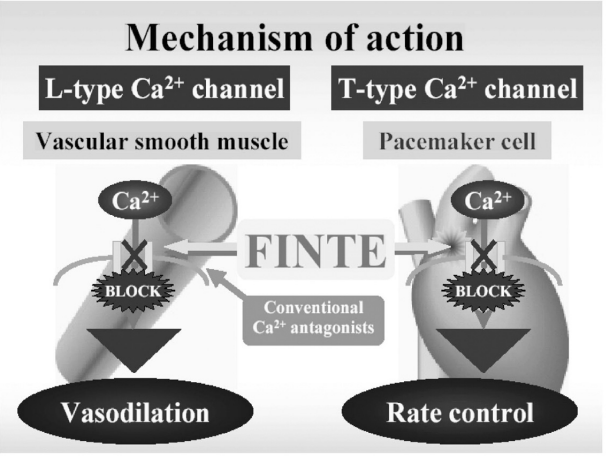
Amlodipine

Why does FINTE show slow-in-onset & long-lasting?



1st step Temporary Storage in phospholipid bilayer
2nd step Slow & Lasting Supply & Bound for DHP site
3rd step Long-lasting Inhibition of Ca^{2+} influx

Mechanism of action



Indication

Hypertension
Renoparenchymal hypertension

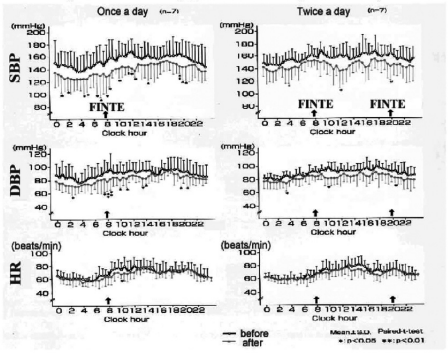
Orally 20-40 mg/once or twice daily doses
The dosage may be increased up to 60 mg/day
if hypotensive effects are insufficient.

Angina pectoris

Orally 40 mg/once a day

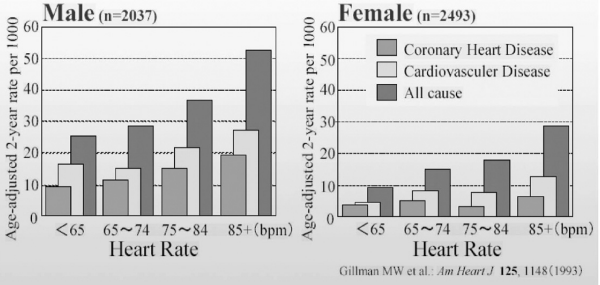
Influences of FINTE on circadian rhythm of BP & HR

(Essential hypertensive patients)



Relation with HR and mortality in patients with hypertension

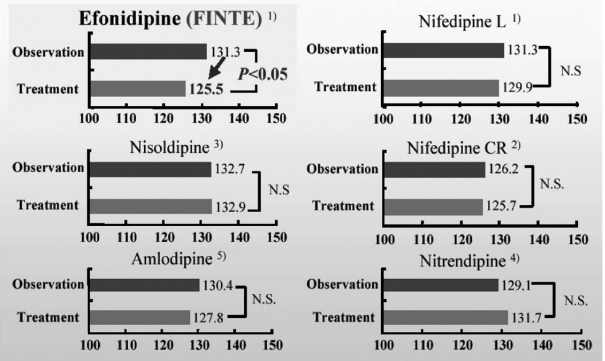
The Framingham Study



Gillman MW et al.: *Am Heart J* **125**, 1148 (1993)

Mortality rate increased by high heart rate

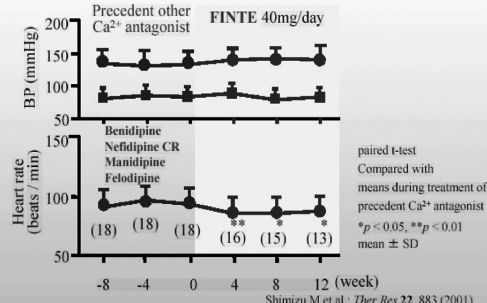
Heart rate at the same time point on exercise tolerance test



1)*Clinical Report* **30**,311-344 (1996) 2) *Jpn Pharmacol Ther* **25**,195-225 (1997) 3) *J Clin Therap Med* **4**,1989-2016 (1988)
4) *J Clin Therap Med* **65**,275-288 (1988) 5) *Clinical Report* **45**,145-164 (1992)

Rate control by FINTE

Effects on BP and HR after switching from precedent other Ca^{2+} antagonists to FINTE



Shimizu M et al : *Ther Res* **22**, 883 (2001)

After switching from precedent other Ca^{2+} antagonists to FINTE, the heart rate had been stably decreased for 12 weeks.

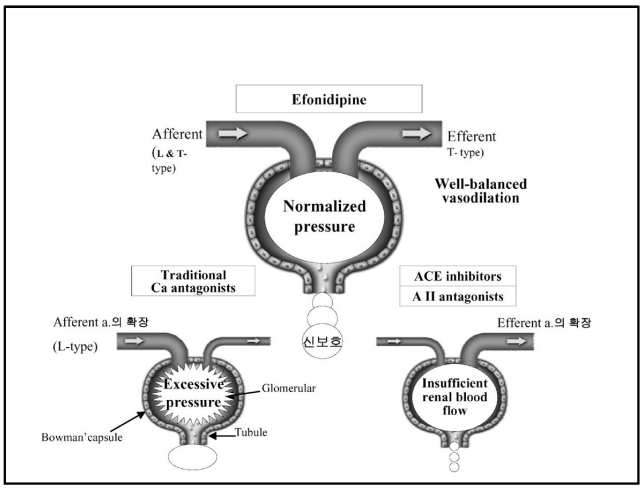
Circ J 2003; 67: 139–145

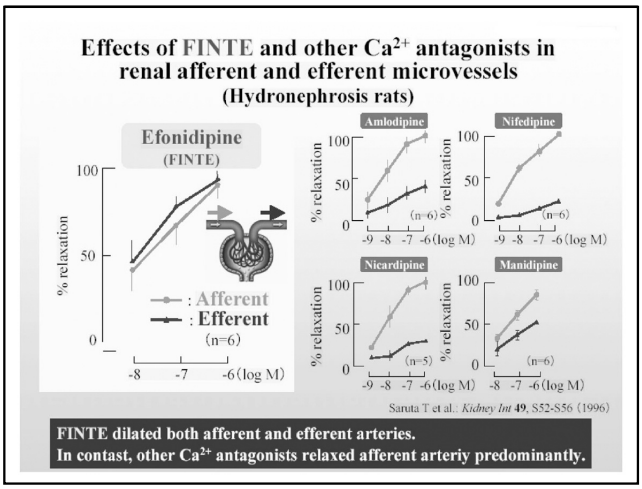
Clinical Efficacy of Efonidipine Hydrochloride, a T-type Calcium Channel Inhibitor, on Sympathetic Activities

— Examination Using Spectral Analysis of Heart Rate/Blood Pressure Variabilities and ^{123}I-Metaiodobenzylguanidine Myocardial Scintigraphy —

Kenji Harada, MD; Masahiro Nomura, MD; Akiyoshi Nishikado, MD; Kouzoh Uehara, MD; Yutaka Nakaya, MD*; Susumu Ito, MD

Dihydropyridine Ca antagonists cause reflex tachycardia related to their hypotensive effects. Efonidipine hydrochloride has inhibitory effects on T-type Ca channels, even as it inhibits reflex tachycardia. In the present study, the influence of efonidipine hydrochloride on heart rate and autonomic nervous function was investigated. Using an electrocardiogram and a tonometric blood pressure measurement, autonomic nervous activity was evaluated using spectral analysis of heart rate/systolic blood pressure variability. Three protocols were used: (1) a single dose of efonidipine hydrochloride was administered orally to healthy subjects with resting heart rate values of 75 beats/min or more (high-HR group) and to healthy subjects with resting heart rate values less than 75 beats/min (low-HR group); (2) efonidipine hydrochloride was newly administered to untreated patients with essential hypertension, and autonomic nervous activity was investigated after a 4-week treatment period; and (3) patients with high heart rate values (≥75 beats/min) who had been treated with a dihydropyridine L-type Ca channel inhibitor for 1 month or more were switched to efonidipine hydrochloride and any changes in autonomic nervous activity were investigated. In all protocols, administration of efonidipine hydrochloride decreased the heart rate in patients with a high heart rate, reduced sympathetic nervous activity, and enhanced parasympathetic nervous activity. In addition, myocardial scintigraphy with ^{123}I-metaiodobenzylguanidine showed significant improvement in the washout rate and H/M ratio of patients who were switched from other dihydropyridine Ca antagonists to efonidipine hydrochloride. Efonidipine hydrochloride inhibits increases in heart rate and has effects on the autonomic nervous system. It may be useful for treating hypertension and angina pectoris, and may also have a cardiac protective function. (*Circ J* 2003; 67: 139–145)





Current Status of Calcium Antagonists in Japan

Takao Saruta, MD

Calcium antagonists comprise the most popular drug class for treatment of hypertension in Japan. More than half of Japanese clinicians use calcium antagonists as initial drug treatment for mild-to-moderate hypertension and, despite recent controversies, their use continues to increase. Nearly a fourth of clinicians use angiotensin-converting enzyme (ACE) inhibitors, and 9% use β-receptor blockers. There are 12 dihydropyridine calcium antagonists and 1 benzothiazepine agent in clinical use. Amlodipine is the most widely used agent in the class. Efonidipine and cilnidipine, recently developed in Japan, both have a slow onset of action and long-lasting hypertensive effect and possess characteristics unique to the class. Efonidipine dilates the efferent as well as the afferent arterioles of the glomerulus; therefore, it appears to have a more pronounced renoprotective effect than other calcium antagonists. Cilnidipine is a dual-channel antagonist, acting on both the peripheral neuronal N-type and vascular L-type calcium channels. It depresses the pressor response to acute cold stress but does not induce tachycardia by hypotensive baroreflex.

Am J Cardiol 1998;82:32R–34R

a slow onset and long duration of action.[8] In humans and rodents, cilnidipine depresses the pressor response to acute cold stress but fails to induce tachycardia evoked by hypotensive baroreflexes.[9] In spontaneously hypertensive rats, cilnidipine also blocks vasoconstriction induced by electrical sympathetic nerve stimulation.[10] In vitro experiments show that cilnidipine inhibits [3H]norepinephrine release evoked by electrical stimulation of the rabbit mesenteric artery.[11] These results suggest that cilnidipine is a dual-channel antagonist that acts on both the neuronal N-type and vascular L-type calcium channels.[12]

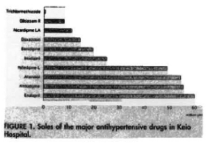
THE INITIAL DRUG FOR THE TREATMENT OF HYPERTENSION IN JAPAN

In Japan, 6 classes of agents—β-receptor blockers, α-receptor blockers, α-β-receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and diuretics—are used for initial pharmacologic treatment of hypertension. According to a 1995 survey of 1,800 Japanese physicians regarding initial drug treatment of hypertension, calcium antagonists are the most widely used (Figure 3).[13] For patients with stage II hypertension (Fifth Joint National Committee [JNC] classification[14]; the Sixth JNC report, subsequently published, was not available at the time of the survey), 52% of the physicians selected calcium antagonists as the initial drug and 23% selected ACE inhibitors; only 4% selected diuretics. For patients with stage III hypertension, 60% of the physicians selected calcium antagonists and 24% selected ACE inhibitors; 4% selected diuretics and 9% β-receptor blockers. For elderly patients with systolic hypertension, preference was greater for calcium antagonists (69%), less for ACE inhibitors (14%), and slightly greater for the diuretics (9%), suggesting that these physicians were taking pathophysiologic characteristics into account when selecting agents in this group.

The results of this survey and data for antihypertensive drug sales in our hospital (Figure 4) suggest that calcium antagonists and ACE inhibitors are still the mainstays of antihypertensive treatment in Japan.

CONCLUSION

In Japan, where stroke is more common than ischemic heart disease as a complication of hypertension, physicians view calcium antagonists as a desirable therapeutic choice. These agents as a class have potent



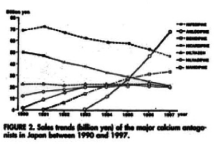


FIGURE 2. Sales trends (billion yen) of the major calcium antagonists in Japan between 1990 and 1997.

effect of efonidipine was similar to that of the DHPs used before the switch to efonidipine therapy, and reflex tachycardia was attenuated.

Conclusion: In this study of a small sample of patients with mild to severe essential hypertension and angina pectoris, efonidipine was as effective as other DHPs. Moreover, the drug attenuated the reflex tachycardia that occurred with traditional DHPs. (*Curr Ther Res Clin Exp.* 2003;64:707–714) Copyright © 2003 Excerpta Medica, Inc.

Key words: hypertension, efonidipine, T-type calcium channel, heart rate, calcium channel blocker, reflex tachycardia.

INTRODUCTION

The usefulness of long-acting calcium channel blockers (CCBs) in the treatment of cardiovascular disease (CVD) is well known. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial[1] (ALLHAT) showed that CCB therapy reduces the complications of hypertension.

In recent years, dihydropyridines (DHPs), a type of CCB, have commonly been prescribed for the treatment of hypertension and angina pectoris. DHPs are effective antihypertensive drugs with minimal serious side effects,[2–4] making them the most popular class of antihypertensive drugs used in Japan. All DHPs act mainly on L-type calcium channels of vessels, which respond quickly, and so may negatively affect cardiac function by activating sympathetic tone,[5–8] which in turn induces an increased heart rate (HR) (reflex tachycardia). Tachycardia is a strong marker of an autonomic abnormality. It accelerates sympathetic tone and decreases vagal activity. Tachycardia, especially in the long term,[9] has been associated with an increased risk for morbidity and mortality from either cardiovascular or noncardiovascular causes in middle-aged (40–<60 years) and elderly (≥60 years) patients with heart failure and/or ischemic heart disease.[9–15]

Two nonselective CCBs, diltiazem and verapamil, block the L-type calcium channels in the vasculature. Therefore, they have a negative inotropic effect. They also have negative chronotropic effects, which may improve the prognosis by preventing the development of heart failure or severe systolic dysfunction.[14,15] On the other hand, because DHPs selectively block the calcium channels in vascular smooth muscle cells, they have little negative inotropic effect. In general, DHPs that have a rapid onset of effect cause reflex tachycardia, while slow-onset and long-acting DHPs have less effect on HR. This has resulted in the widespread use of long-acting DHPs that have no acute hypotensive action.

T-type calcium channels in the sinoatrial node attenuate elevated HR by participating in cardiac pacing in the sinoatrial node cells. Therefore, L- and T-type CCBs (eg, efonidipine hydrochloride) may favorably affect cardiac pacing, thereby reducing reflex tachycardia. Mibefradil, which does not affect L-type channels, has been described in many studies[16–19] as having clinically beneficial

TABLE I Efficacy and Adverse Effects of Calcium Antagonists in Japan (Results Before Marketing)

Agent	Incidence of AEs, n (%)	Flushing (%)	Headache (%)	Antihypertensive Efficacy
Nifedipine L (n = 822)	137 (16.7)	10.5	1.6	75–80
Nicardipine LA (n = 624)	60 (9.6)	1.8	2.4	70–75
Nitrendipine (n = 1,434)	173 (12.1)	4.6	3.2	70–75
Nisoldipine (n = 919)	143 (15.6)	7	4	70–75
Nilvadipine (n = 1,104)	140 (12.7)	5.8	3.2	70–75
Manidipine (n = 865)	90 (10.4)	2.7	1.5	70–75
Barnidipine (n = 865)	122 (14.1)	3.4	2.1	75–80
Benidipine (n = 897)	60 (6.7)	1.3	1.4	75–80
Amlodipine (n = 1,103)	65 (5.9)	1.2	0.4	75–80
Efonidipine (n = 703)	49 (7)	1.8	1.3	75–80
Cilnidipine (n = 764)	76 (9.7)	4.5	3.7	75–80
Felodipine (n = 820)	137 (16.7)	5.7	5.6	75–80
Aranidipine (n = 703)	81 (11.5)	2.4	4.1	75–80
Nifedipine CR (n = 704)	84 (12)	4.6	4.1	80–85
Diltiazem R (n = 3,577)	74 (2.1)	0.1	0.4	65–70

AEs = adverse effects.

Effect of Efonidipine and ACE Inhibitors on Proteinuria in Human Hypertension With Renal Impairment

Koichi Hayashi, Hiroo Kumagai, and Takao Saruta

Background: Although several lines of recent studies fail to demonstrate the beneficial action of calcium antagonists, a novel dihydropyridine efonidipine, which possesses dilatory action of both afferent and efferent arterioles and, therefore, shares the renal microvascular action with angiotensin converting enzyme (ACE) inhibitors, is reported to exhibit renal protection in experimental animals.

Methods: The present study evaluated the effect of efonidipine and ACE inhibitors on blood pressure (BP) and proteinuria. Sixty-eight hypertensive patients with renal impairment (serum creatinine, >1.5 mg/dL) or chronic renal parenchymal disease were randomly assigned to efonidipine or ACE inhibitor treatment. Of the 68 patients, 23 were treated with efonidipine and 20 with ACE inhibitors; these patients were analyzed for the 48-week study.

Results: Both efonidipine and ACE inhibitors produced a similar degree of reductions in BP (efonidipine, from 161 ± 2/93 ± 2 to 142 ± 5/82 ± 2 mm Hg; ACE inhibitor, from 163 ± 3/95 ± 2 to 141 ± 5/83 ± 2 mm Hg), and maintained creatinine clearance for 48 weeks. Proteinuria tended to decrease in both groups, and a significant reduction was observed in proteinuric patients (>1 g/day) (efonidipine, from 2.7 ± 0.3 to 2.1 ± 0.3 g/day; ACE inhibitor, from 3.0 ± 0.4 to 2.0 ± 0.5 g/day). Of interest, efonidipine decreased proteinuria in proteinuric patients who failed to manifest decreases in systemic BP. Finally, the incidence of adverse effects, including hyperkalemia and cough, was less in the efonidipine-treated group.

Conclusions: Both efonidipine and ACE inhibitors preserved renal function in hypertensive patients with renal impairment. The antiproteinuric effect was apparent in patients with greater proteinuria. The beneficial action of efonidipine, along with fewer side effects, may favor the use of this agent in the treatment of hypertension with renal impairment. Am J Hypertens 2003;16:116–122

Key Words: Efonidipine, ACE inhibitors, renal disease, proteinuria, hypertension.

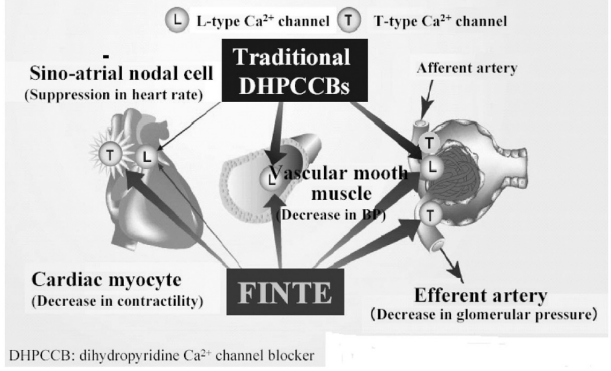
ORIGINAL ARTICLE

Effects of efonidipine on platelet and monocyte activation markers in hypertensive patients with and without type 2 diabetes mellitus

S Nomura, S Kanazawa and S Fukuhara
First Department of Internal Medicine, Kansai Medical University, Osaka, Japan

We compared the levels of microparticles, platelet activation markers, soluble cell adhesion molecules, and soluble selectins between hypertensive patients with and without type 2 diabetes and control subjects. Binding of anti-glycoprotein IIb/IIIa and anti-glycoprotein Ib monoclonal antibodies to platelets did not differ significantly between the hypertensive patients and controls, but platelet expression of activation markers (CD62P, CD63, PAC-1, and annexin V) was higher in the hypertensive patients. Platelet-derived microparticle (PDMP) and monocyte-derived microparticle (MDMP) levels were significantly higher in the hypertensive patients than in the controls. Soluble ICAM-1, VCAM-1, P-selectin, and E-selectin levels were also higher in the hypertensive patients, and they were significantly higher in the hypertensive patients with diabetes. After treatment with efonidipine, the levels of PDMPs, CD62P-, CD63-, PAC-1-, and annexin V-positive platelets, sICAM-1, sVCAM-1, sP-selectin, and sE-selectin all decreased significantly. The MDMP levels decreased, and the decrease was significant in the hypertensive patients with diabetes. These findings suggest that administration of efonidipine to hypertension patients with diabetes may prevent the development of cardiovascular complications caused by cell adhesion molecules or activated platelets and monocytes.
Journal of Human Hypertension (2002) **16**, 539–547.
doi:10.1038/sj.jhh.1001447

Action site of major DHPCCBs and Ca^{2+} channel



DHPCCB: dihydropyridine Ca^{2+} channel blocker

Main Adverse Effect

Palpitation	1.3%
Heat	1.1%
Hot Flushing	0.8%
Brady Cardia	0.1%

Good Indications for 3rd Generation CCB (esp. Finte)

- **HT with Stable or Unstable Angina**
- **HT with Asthma or COPD**
- **HT with PAD or Dementia**
- **HT with Nephropathy**
- **HT with CHF**