Effects of Efonidipine, an L- and T-Type Dual Calcium Channel Blocker, on Heart Rate and Blood Pressure in Patients with Mild to Severe Hypertension: An Uncontrolled, Open-Label Pilot Study

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ABSTRACT

Background: Dihydropyridines (DHPs), a type of calcium channel blocker (CCB), are commonly prescribed for the treatment of hypertension and angina pectoris. DHPs act mainly on L-type calcium channels, essentially causing reflex tachycardia (elevated heart rate [HR]), which negatively affects cardiac function. Because T-type calcium channels in the sinoatrial node attenuate reflex tachycardia, a dual L- and T-type CCB (eg, efonidipine hydrochloride) may favorably affect cardiac pacing, thereby reducing reflex tachycardia. The effect of efonidipine as a DHP on HR deserves special consideration with regard to reflex tachycardia.

Objective: The aim of this study was to determine whether the L- and T-type CCB efonidipine can decrease the elevated HR induced by prior treatment using traditional DHPs.

Methods: This uncontrolled, open-label pilot study was conducted at the Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine (Tokyo, Japan). Patients aged 48 to 80 years with mild to severe hypertension and angina pectoris and who were receiving therapy with a DHP other than efonidipine were eligible. During an 8-week observation period, patients continued therapy with their DHP. After those 8 weeks, therapy was switched to oral efonidipine (40-mg tablet once daily) in patients whose blood pressure (BP) was stable and well controlled and whose HR was >80 bpm. BP and HR were monitored every 4 weeks of treatment with efonidipine.

Results: Eighteen patients (12 men, 6 women; mean [SD] age, 62.6 [12] years) were enrolled. After the switch to efonidipine, mean (SD) HR decreased significantly, from 94 (7) bpm to 86 (11) bpm at 12 weeks ($P < 0.05$). The antihypertensive

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 Trial¹ (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.^{9–13}

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

effects on CVD. These benefits are supposedly produced by its T-type calcium channel blocking action. Unfortunately, the drug has been withdrawn from clinical use because of potential drug interactions.

Efonidipine, an antihypertensive and antianginal agent with a 1,4-dihydropyridine 5-phosphonate structure, acts on both T- and L-type calcium channels, which may produce effects similar to those of mibefradil. Efonidipine has been described as having a chronotropic effect, which may suppress tachycardia.¹³ Working on sinoatrial node cells by inhibiting T-type calcium channel activation or negative chronotropic effect, efonidipine prolongs the late phase-4 depolarization of the sinoatrial node action potential, which suppresses elevated HR.¹³ An analysis of postmarketing surveillance of efonidipine (unpublished data, Shionogi & Co., Ltd., 2002) revealed an HR reduction in patients with a baseline HR >70 bpm. The effect of efonidipine on HR deserves additional consideration with regard to reflex tachycardia.

The aim of this pilot study was to determine whether the L- and T-type CCB efonidipine can decrease the elevated HR induced by prior treatment using traditional DHPs.

PATIENTS AND METHODS

Patients

This uncontrolled, open-label pilot study was conducted at the Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine (Tokyo, Japan). Patients aged 48 to 80 years with mild to severe essential hypertension (systolic blood pressure [BP] [SBP]/diastolic BP [DBP] >140/>90 mm Hg) and angina pectoris who had been receiving antihypertensive treatment with a long-acting DHP other than efonidipine (eg, amlodipine besylate, barnidipine, benidipine hydrochloride, felodipine, manidipine hydrochloride, nifedipine) for >1 year were eligible. All of the patients were referred by physicians practicing in or near Tokyo, Japan. Verbal informed consent was provided by all patients. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study. Women of childbearing age were required to use an effective method of birth control throughout the study because of possible teratogenic effects.

Methods

During an 8-week observation period, BP and HR were monitored while patients continued their existing therapy with the DHP. At week 0 (baseline), patients were switched to oral efonidipine (40-mg tablet once daily for 12 weeks) if their BP had been stable and well controlled (SBP/DBP $\leq$ 140/ $\leq$ 90 mm Hg) and their HR was >80 bpm during the prior 8 weeks. Other medications remained unchanged during the study period.

BP and HR were measured by a physician every 4 weeks during the treatment period, with the patient in a sitting position after resting for $\geq$ 15 minutes.

BP was measured using a sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan). In our study, *reflex tachycardia* was defined as HR >80 bpm for >2 months. Compliance was confirmed using patient interview.

Statistical Analysis

The differences in BP and HR between the observation and treatment periods were analyzed, when appropriate, using the paired Student *t* test. $P \leq 0.05$ was considered statistically significant.

RESULTS

Eighteen Japanese patients (12 men, 6 women; mean [SD] age, 62.6 [12] years) were enrolled in the study, as shown in Table I. Table I also shows the DHP and dose each patient was receiving before entering the study.

Table II shows the BP and HR of each patient during the observation period and during the 12 weeks of treatment with efonidipine. The figure shows mean (SD) BP and HR during the observation and treatment periods. No significant differences in mean BP were found between the observation period and any time point after switching to efonidipine.

Table I. Patient characteristics and background medication during the observation period.

Patient No.	Age, y	Sex	Medication	Dose, mg	Concomitant Disease
1	78	F	Manidipine	10	IHD
2	58	M	Benidipine	8	—
3	47	M	Benidipine	8	—
4	59	M	Manidipine	10	HL
5	76	F	Benidipine	8	—
6	48	M	Nifedipine-L	20	—
7	80	F	Nifedipine-L	20	—
8	54	M	Nifedipine-CR	40	HL
9	64	F	Nifedipine-CR	40	—
10	72	M	Benidipine	4	HL
11	50	M	Benidipine	4	HUA
12	55	F	Nifedipine-CR	40	HL
13	51	M	Felodipine	5	DM
14	67	M	Benidipine	8	—
15	60	M	Amlodipine	5	HL
16	80	M	Barnidipine	4	—
17	78	F	Benidipine	4	—
18	50	M	Amlodipine	5	—

F = female; IHD = ischemic heart disease; M = male; HL = hyperlipidemia; L = long acting; CR = continuous release; HUA = hyperuricemia; DM = diabetes mellitus.

Table II. Blood pressure (mm Hg) and heart rate (bpm) of each patient during the observation period (weeks –8 to 0) and the efonidipine treatment period (weeks 0 to 12).

Patient No.	Study Week																	
	–8			–4			0			4			8			12		
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR
1	141	67	93	103	59	91	137	70	91	141	83	85	141	73	88	166	75	78
2	135	95	92	120	101	86	122	87	100	154	103	90	128	92	88	144	103	97
3	–	–	–	114	76	88	130	85	87	–	–	–	123	85	80	–	–	–
4	148	89	81	136	81	88	136	84	87	127	86	72	149	96	74	149	84	72
5	135	85	101	137	83	96	146	88	103	148	96	82	145	96	90	164	95	71
6	117	77	108	122	81	96	132	84	93	125	92	94	130	91	88	–	–	–
7	133	86	105	139	98	119	128	97	111	123	94	88	–	–	–	–	–	–
8	116	63	93	118	99	92	121	75	95	106	66	82	131	87	84	88	72	80
9	–	–	–	116	83	91	108	71	102	135	89	93	113	79	97	146	97	103
10	–	–	–	149	93	96	155	77	87	–	–	–	142	66	83	143	73	91
11	142	89	81	139	91	88	141	91	93	128	91	92	148	95	101	–	–	–
12	147	95	91	133	94	89	153	105	97	151	111	99	151	89	66	139	84	94
13	135	96	83	121	86	104	–	–	–	146	91	85	–	–	–	–	–	–
14	145	82	89	116	80	100	134	79	92	149	87	92	154	80	86	159	88	76
15	156	80	107	174	100	96	141	86	107	140	84	94	146	77	91	130	76	90
16	142	78	88	160	75	85	150	79	83	164	81	83	147	61	89	124	64	87
17	143	84	91	166	98	113	147	82	91	159	73	89	123	63	93	132	69	103
18	135	84	70	119	88	80	144	85	92	146	101	74	144	79	79	142	95	76

SBP = systolic blood pressure (normal value, ≤ 140 mm Hg); DBP = diastolic blood pressure (normal value, ≤ 90 mm Hg); HR = heart rate (normal value, ≤ 70 bpm).

Figure. Mean (SD) (A) blood pressure (BP) and (B) heart rate (HR) during the observation period (study weeks -8 to 0) and the efonidipine treatment period (study weeks 0 to 12). SBP = systolic BP; DBP = diastolic BP. * $P < 0.01$ versus week 0. † $P < 0.05$ versus week 0.

Mean (SD) HR during the observation period ($n = 18$) was 94 (7) bpm. After the switch to efonidipine, it was significantly lower at 4 weeks (87 [7] bpm; $P < 0.01$ vs baseline), 8 weeks (86 [9] bpm; $P < 0.05$ vs baseline), and 12 weeks (86 [11] bpm; $P < 0.05$ vs baseline). Reflex tachycardia was attenuated in all patients throughout the study.

Some patients did not return to the hospital for every scheduled visit; however, all patients received the medication for the full 12-week treatment period.

DISCUSSION

Interestingly, most DHPs have been shown to cause reflex tachycardia.¹⁰ In the present study, all the DHPs used during the observation period were long-acting agents that caused reflex tachycardia. Efonidipine caused no reflex tachycardia

throughout the treatment period, while providing the same excellent antihypertensive effect as the other DHPs used during the observation period. This lack of reflex tachycardia with efonidipine may be due to its T-type calcium channel blocking action.

The favorable results produced by efonidipine in this study must be interpreted carefully because the study was conducted with a small number of patients. Although the HR was decreased with efonidipine, it is not clear whether this decreased HR is clinically significant. Additional studies using a control group and random allocation to treatment are needed. The impact of efonidipine on morbidity and mortality must be more closely examined in a long-term follow-up study of its efficacy and tolerability using a larger number of patients with hypertension or angina pectoris.

CONCLUSIONS

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 other DHPs.

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