A Study on the Effects of Nifedipine in Hypertensive Crises and Severe Hypertension

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SUMMARY

Ten mg of Nifedipine, a Ca^{++} antagonist, was administered orally in 2 groups of patients; Group I: 6 patients in hypertensive emergency and Group II: 12 patients with intractable, severe hypertension. Following results were obtained. 1) A marked hypotensive effect was observed in all patients of Group I. The maximum effect was observed within 30 to 60 min and lasted for approximately 180 min. Clinical symptoms also improved remarkably with the fall in blood pressure. Any side effect was not observed. 2) A marked hypotensive effect was observed in all cases of Group II. The blood pressure fell by 21.4% systolic ($p < 0.01$) and 19.4% diastolic ($p < 0.02$). The peripheral vascular resistance also showed the decrease by 26.2% ($p < 0.01$). The heart rate and cardiac index increased slightly.

It was suggested that the hypotensive mechanism of this preparation is due primarily to the peripheral vasodilatation.

Additional Indexing Words:

Ca^{++} antagonists Hemodynamics in hypertension Left ventricular dimension on echocardiogram Hypertensive emergency
Intractable hypertension

DRUGS pharmacologically acting as Ca^{++} antagonists have so far been mainly used in the treatment of coronary heart disease. Nifedipine, 4-(2'-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxy-dimethyl-ester, was investigated as to its hypotensive effect by Murakami¹⁾ and Aoki²⁾ and their co-workers, in addition to its established antianginal action.

In an open trial, we administered Nifedipine to patients in hypertensive emergencies, and with prolonged, severe hypertension, not responding to other standard hypotensives.

Besides the blood pressure lowering action of Nifedipine, hemodynamic

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changes and occurrence of adverse reactions attributable to the drug were investigated.

STUDY GROUP AND METHOD

Eighteen patients, 11 men and 7 women, from 35 to 85 years old (mean age ; 63.1), admitted to Tokyo Metropolitan Geriatric Hospital were selected for the trial. These patients were divided into the following groups ;

Group I (hypertensive crises) consisted of 3 men and 3 women, 64–77 years old (mean age 69.5), with a sudden, marked rise in blood pressure, accompanied by clinical symptoms suggestive of hypertensive encephalopathy such as disturbances of consciousness and convulsions, requiring emergency measures to lower the elevated blood pressure.

Underlying disorders in these cases were cerebrovascular accident in 3 patients, renal insufficiency in 1 and unknown in other 2 patients.

Blood pressure before treatment with Nifedipine was, on the average, 236.7 mmHg (range : from 202 to 290 mmHg) systolic and 109.7 mmHg (range : from 80 to 150 mmHg) diastolic. After measuring blood pressure and pulse rate, 10 mg of Nifedipine were administered orally. Three patients with disturbance of consciousness received the drug dissolved in 10 ml of water via a gastric tube. Blood pressure was recorded 30, 60, 120, and 180 min after oral administration. Three patients, who received Nifedipine via a gastric tube had an additional blood pressure measurement 10 min after the administration.

Group II (severe hypertension) consisted of 8 men and 4 women from 35 to 85 years old (mean age ; 59.9) with blood pressure exceeding 200 mmHg systolic or exceeding 110 mmHg diastolic, persisting for more than 1 month. The patients could not be managed by mono- or combination therapy with thiazide, α -methyl dopa, β -blocker or hydralazine. Nine patients were diagnosed as essential hypertension, 2 as renovascular hypertension, and 1 as renal hypertension.

Blood pressure before therapy with Nifedipine was, on the average, 205.1 mmHg (range ; from 170 to 226 mmHg) systolic and 113.3 mmHg (range ; from 90 to 140 mmHg) diastolic. Blood pressure, heart rate and following hemodynamic parameters were measured before and 30 min after oral administration of Nifedipine. Left ventricular dimensions in end-diastole and in end-systole were measured and ejection fraction was calculated on echocardiogram recorded by Aloka SSD 110 in 8 patients before and after the drug administration.

Circulating blood volume was determined by injection of Evans blue with patients in supine position. Cardiac output was measured by dye dilution method with indocyanine green. Dye dilution curve was recorded with Elma-Densitograph EN 80 and cardiac output was calculated with Elma-Computer EW 90.

RESULTS

Group I; As shown in Fig. 1, a marked hypotensive effect was observed in all cases within 60 min after the administration of Nifedipine. In 3 patients with gastric intubation, a fall of blood pressure occurred 10 min after the

Fig. 1. Effect of Nifedipine in hypertensive crises.

※: via a gastric tube.

Fig. 2. Time course of blood pressure and pulse rate following oral administration of Nifedipine. Bars denote mean values $\pm$ SEM.

administration of the drug. With a fall of blood pressure, all patients showed improvement of their clinical symptoms. Adverse drug reactions attributable to Nifedipine therapy were not observed.

Blood pressure and pulse rate before administration of Nifedipine and their changes up to 180 min after the drug administration are shown in Fig. 2. The maximum hypotensive effect was obtained within 30 to 60 min and lasted for over 180 min. Pulse rate showed no significant changes (Table I).

Following is a representative case; (Case 5; K.T.)

A 72-year-old man developed left hemiplegia due to cerebral apoplexy on September 18, 1976. In December 1976, he was admitted to Tokyo Metropolitan Geriatric Hospital for rehabilitation training.

Table I. Time Course of Blood Pressure and Heart Rate after Nifedipine in Hypertensive Emergency

No.	Name, Age and Sex	Cause of Hypertension	Before			10 min			30 min		
			SBP mmHg	DBP mmHg	MBP mmHg	HR b/m	SBP mmHg	DBP mmHg	MBP mmHg	HR b/m	HR b/m
1	S.A. 77 F	Unknown	290	150	196.7	68	—	—	—	180	100
2	S.S. 66 M	APO (GT)	258	88	144.7	86	182	80	114.0	170	80
3	S.O. 73 M	Unknown	230	120	156.7	—	—	—	—	180	96
4	I.M. 64 F	APO (GT)	210	80	123.3	92	158	62	94.0	148	58
5	K.T. 72 M	APO (GT)	230	110	150.0	110	146	84	104.3	120	65
6	T.S. 65 F	RHT	202	110	140.7	—	—	—	—	140	80
means±SE			236.7 13.3	109.7 10.1	152.0 10.0	89.0 8.7	161.9 10.8	75.3 6.8	104.1 5.8	149.7 13.7	73.2 9.5
No.	Name, Age and Sex	Cause of Hypertension	60 min			120 min			180 min		
			SBP mmHg	DBP mmHg	MBP mmHg	HR b/m	SBP mmHg	DBP mmHg	MBP mmHg	HR b/m	HR b/m
1	S.A. 77 F	Unknown	170	110	130.0	66	162	90	114.0	164	90
2	S.S. 66 M	APO (GT)	160	70	100.0	90	190	80	116.7	210	90
3	S.O. 73 M	Unknown	150	80	103.0	—	186	90	122.0	202	100
4	I.M. 64 F	APO (GT)	158	50	86.0	88	146	70	95.3	172	90
5	K.T. 72 M	APO (GT)	120	66	83.3	105	110	60	76.7	188	92
6	T.S. 65 F	RHT	140	80	100.0	—	—	—	—	—	—
means±SE			149.7 7.2	75.8 8.2	100.4 6.8	87.0 7.9	158.8 14.6	78.0 5.8	104.9 8.4	187.0 11.2	92.5 2.5

Abbreviation: SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, MBP= Mean Blood Pressure, HR= Heart Rate, EHT= Essential Hypertension, APO= Apoplexy, RHT= Renal Hypertension, GT= Via a Gastric Tube

Physical examination on admission revealed blood pressure 166/86 mmHg, heart rate 88/min regular, no abnormalities on cardiac and pulmonary auscultation, mild dementia, left hemiplegia and presence of pseudobulbar paralysis. Cardiothoracic ratio was 60% on the chest X-ray film and the electrocardiogram showed left ventricular hypertrophy.

After the admission, the patient's blood pressure ranged from 120 to 160

Fig. 3. Hemodynamic changes 30 min after Nifedipine in severe hypertension. * $p < 0.02$, ** $p < 0.01$.

Fig. 4. Changes of hemodynamic parameters in per cent after Nifedipine in severe hypertension.

Table II. Hemodynamic Values before and 30 min after Nifedipine in Severe Hypertension

No.	Name, Age and Sex	Cause of Hypertension	SBP (mmHg)	DBP (mmHg)	MBP (mmHg)	HR beats/min	CI L/min/M ²	SI ml/beat/M ²	TPRI dyne-sec/cm ⁵ .M ²	Ds (mm)	Dd (mm)	EF
1	N.O. 65F	RVHT	before	136	166.0	74	2.61	35.4	5069			
			after	180	130.0	90	2.98	33.1	3517			
			%	-20.4	-22.1	+21.6	+13.7	-6.5	-30.7			
2	N.K. 62F	EHT	before	110	143.0	53	2.63	49.6	4352	35.2	50.0	0.65
			after	94	123.0	70	3.14	44.9	3136	33.2	48.2	0.76
			%	-13.4	-14.6	+32.0	+19.3	-9.4	-28.0	-5.7	-3.6	+16.9
3	K.O. 62M	RVHT	before	140	164.0	94	2.47	26.3	5344	23.0	46.0	0.88
			after	184	134.0	98	3.52	35.9	3072	23.0	46.0	0.88
			%	-14.1	-21.4	+4.2	+42.5	+36.5	-42.6	0	0	0
4	T.S. 51M	RHT	before	130	156.0	64	2.56	40.0	4904			
			after	160	128.0	75	2.00	26.6	5120			
			%	-23.9	-13.9	+17.1	-21.9	-33.5	+4.4			
5	T.B. 43M	EHT	before	170	130.0	85	3.33	39.2	3120	30.0	40.0	0.58
			after	150	96.0	75	2.83	37.7	2744	28.0	40.0	0.66
			%	-11.8	-36.4	-26.2	-15.1	-3.9	-12.1	-6.7	0	+13.8
6	S.I. 60F	EHT	before	200	133.0	51	2.76	54.1	3856	30.0	42.0	0.64
			after	110	56	62	3.23	52.1	1832	30.0	50.0	0.78
			%	-45.0	-44.0	+21.5	+17.0	-3.7	-52.5	0	+19.0	+21.9
7	K.M. 35M	EHT	before	206	112	72	3.07	43.6	3966	27.0	49.0	0.84
			after	162	92	80	3.28	42.5	2733	25.0	49.0	0.86
			%	-21.0	-19.0	+11.1	+6.8	-2.6	-32.0	-7.5	0	+2.4

8	Y.E.	85M	EHT	before after %	190 138 -27.4	90 88 -2.3	123.0 104.0 -15.5	83 73 -12.1	2.69 3.03 +12.0	32.4 41.5 +28.0	3656 2700 -25.7	38.0 35.0 -7.9	52.0 50.0 -3.9	0.60 0.66 +10.6
9	E.F.	64M	EHT	before after %	216 180 -16.7	108 98 -9.3	144.0 125.0 -13.2	67 78 +16.4	2.73 2.58 -5.5	40.7 33.5 -17.7	4216 3872 -8.2	22.0 22.0 0	41.0 41.0 0	0.84 0.84 0
10	N.K.	43M	EHT	before after %	204 190 -6.9	130 122 -6.2	154.0 144.0 -6.5	96 102 +6.2	5.03 4.96 -1.4	52.4 48.6 -7.3	2994 2336 -22.0	32.0 33.0 +3.1	51.0 51.0 0	0.75 0.73 -6.7
11	O.M.	69M	EHT	before after %	206 160 -22.4	96 80 -16.7	132.0 106.0 -19.7	64 76 +18.7	3.61 3.84 +6.3	56.4 50.5 -10.5	2944 2232 -24.2			
12	K.M.	80F	EHT	before after %	210 140 -33.4	96 70 -27.1	134.0 93.0 -30.6	64 75 +17.1	3.38 4.00 +18.3	52.8 53.3 +0.9	3168 1864 -41.2			
MEAN				before (m ± se)	205.1 4.5	113.3 5.4	143.5 4.6	72.3 4.6	3.07 0.23	43.6 3.0	3965.7 263.8	29.7 2.0	46.4 1.7	0.72 0.04
				after (m ± se)	161.8 7.7	91.5 6.2	114.3 6.4	79.5 3.7	3.28 0.24	42.5 2.8	2931.5 266.7	28.7 1.8	46.9 1.5	0.77 0.09
				% (m ± se) t	-21.4 3.0 p<0.01	-19.4 3.5 p<0.02	-20.8 2.8 p<0.02	+10.0 3.8 n.s.	+6.8 5.0 n.s.	-2.5 5.4 n.s.	-26.2 4.5 p<0.01	-3.1 1.5 n.s.	+1.4 2.6 n.s.	+7.4 3.5 n.s.

Abbreviation: CI=Cardiac Index, SI=Stroke Index, TPRI=Total Peripheral Resistance Index, Ds=Systolic Dimension of Left Ventricle, Dd=Diastolic Dimension of Left Ventricle, EF=Ejection Fraction, RVHT=Renovascular Hypertension.

mmHg systolic and from 70 to 96 mmHg diastolic without any hypotensive agent. Rehabilitation training had been continued uneventfully until January 8, 1977 when the patient suddenly developed coarse tremor in the right lower and upper extremities, disturbance of consciousness and positive Babinski's reflex on the right side. Simultaneously, blood pressure rose sharply to 230/110 mmHg and intramuscular injection of 0.3 mg of Reserpine was ineffective. Then, 10 mg of Nifedipine dissolved in 10 ml of water was administered via a gastric tube. Ten min later, blood pressures fell to 145/84 mmHg, consciousness became clear and tremors disappeared.

Mild paralysis persisted in the right upper and lower extremities, but otherwise recovery was uneventful. Blood pressure remained within normal limit thereafter.

Since urinary excretion of catecholamine and VMA were normal, possibility of pheochromocytoma could be ruled out and electro-encephalogram showed no evidence of epilepsy. This episode was diagnosed as a recurrent attack of cerebrovascular accident.

Group II; In Figs. 3 and 4, changes in blood pressure, heart rate, cardiac index, stroke volume and left ventricular dimension following administration of Nifedipine in patients with severe hypertension are shown.

All patients of this group responded to the therapy with a marked lowering of systolic pressure, on the average, from 205.1 mmHg (range; 170–226 mmHg) to 161.8 mmHg (range; 110–190 mmHg) ($p < 0.01$) and from 113.3 mmHg (range; 90–140 mmHg) to 91.5 mmHg (range; 56–112 mmHg) ($p < 0.02$) diastolic (Table II).

Heart rate increased in 10 patients and decreased slightly in 2, but the increase from 72.3 to 79.5 beats per minute, on the average, was not statistically significant.

Cardiac index increased in 8 patients, showing a tendency of slight rise by 6.8% from 3.07 to 3.28 L/min/M² on the average (n.s.).

Stroke index decreased only slightly in 9 patients from 43.6 to 42.5 ml/beat/M² on the average, but not significantly.

Total peripheral resistance fell markedly in all cases except 1 case (Case 4) from an average of 3965.7 to 2931.5 dynes-sec-cm² or 26.2% reduction ($p < 0.01$).

Left ventricular end-diastolic dimension on echocardiogram increased in 1 case (Case 6), but remained uncanged or decreased slightly in other 7 patients. Left ventricular end-systolic dimension decreased in 4, increased slightly in 1, and remained uncanged in 3 patients. Ejection fraction increased in 5, remained unchanged in 2 patients and decreased in 1. No side effects were observed, except flushing sensation in 1 case (Case 12).

The following is a representative case; (Case 9, E.F.) (Fig. 5).

A 64-year-old man was admitted to the hospital for treatment of severe hyper-

Fig. 5. Treatment and change of blood pressure during hospitalization in case 9 (E.F.).

TCM= Trichlormethiazide, PROP= Propranolol, HYDRAL= Hydralazine, NFD= Nifedipine.

tension. His hypertension had been documented for at least 20 years, and treated with various anti-hypertensive agents unsuccessfully.

On admission on March 25, 1976, the pulse rate was 80 beats per minute and blood pressure was 226/130 mmHg, without postural hypotension. The other physical abnormalities included left hemiparesis due to cerebrovascular accident which developed 3 years ago and hypertensive retinopathy of grade 3 (Keith-Wegener's classification.)

Cardio-thoracic ratio was 62.4% and the electrocardiogram showed left ventricular hypertrophy. Laboratory data included hemoglobin concentration of 16.2 Gm/100 ml, blood urea nitrogen (BUN) 15.9 mg/100 ml, serum creatinine 1.2 mg/100 ml, serum Na 144 mEq/L, K 3.5 mEq/L, Cl 101 mEq/L, urinalysis showed no abnormal finding and excretion of VMA was within normal limit. Secondary hypertension was excluded by other clinical and laboratory data during the admission.

The patient was given a combination therapy of 4 mg of trichlormethiazide, 60 mg of propranolol, and 90 mg of hydralazine in addition to a low salt diet, but his blood pressure fell only slightly. Following the combination therapy, oral administration of Nifedipine 10 mg was started on June 15, 1976.

When the drug was taken at 8 a.m., blood pressure measurement at 10 a.m. showed a marked fall as shown in Fig. 5.

The hypotensive effects lasted for only 5 to 6 hours. In order to obtain a sustained hypotensive effect, the patient was instructed to take 10 mg of Nifedipine orally every 6 hours.

He was discharged thereafter and has been followed in the out-patient clinic. The hypotensive effect of Nifedipine has not decreased, nor are adverse drug reactions observed.

DISCUSSION

Studies on the hypotensive effect of Nifedipine have been reported by Vater³⁾ and Stoepel⁴⁾ in animal experiments and by Murakami¹⁾ and Aoki²⁾ in clinical trials.

In all these reports, the drug was used in cases with mild to moderate hypertension. No report is available on the use of Nifedipine in hypertensive crises or in severe intractable hypertension.

At present, injection of hydralazine, diazoxide, minoxidil or sodium nitropruside is usually used in hypertensive emergencies in Europe and America.⁵⁾ Although the injection of hydralazine, diazoxide or minoxidil has a rapid and remarkable hypotensive effect, it causes a reflex tachycardia and therefore have to be given with caution in cases complicated by coronary artery disease.⁶⁾ Moreover, these drugs except hydralazine are not available in Japan, so they are not used in the clinical management of hypertensive emergency.

In the present study, Nifedipine, even when administered orally, showed rapid fall in blood pressure in these hypertensive states. Onset of effect was already observed in 30 min when capsules were taken orally and within 10 min when it was diluted in water and given via a gastric tube. Thus, in the case of hypertensive encephalopathy with disturbance of consciousness, the content of a capsule could be given by gastric intubation successfully.

Despite a marked fall in blood pressure in a short period of time, a reflex tachycardia rarely occurred, subjective symptoms caused by the fall in blood pressure was not observed and clinical symptoms accompanying hypertension were improved remarkably.

However, the duration of the hypotensive effect was relatively short, with a maximum effect within 30 to 60 min and became less marked after 180 min. In our clinical trial, a follow-up of more than 3 hours was not done. Aoki et al⁷⁾, however, reported that the effect of Nifedipine persisted for 7 to 8 hours when 30 mg was given orally.

At present, a combination of hydralazine, bethanidine and/or guanethidine are widely used as anti-hypertensive agents for severe hypertension. But, there are cases in whom these drugs are ineffective or their use is limited due to side-effects.

Nifedipine was proved to be effective in hypertension refractory to these conventional anti-hypertensives. All 12 cases in our study responded to the therapy with a decrease of blood pressure by 21.4% systolic and 19.4% diastolic.

A 10.0% increase in heart rate along with a fall in blood pressure were

recorded, which is in agreement with findings reported by Murakami¹¹⁾ and Aoki.²⁾ Aoki and co-workers²⁾ interpret the increase in heart rate as due to augmented activity of sympathetic nervous system, since it occurred in parallel with a rise in plasma renin activity.

Cardiac index increased by 6.8% in this study. According to studies of Lydtin et al⁸⁾ in normal volunteers, a fall in blood pressure and reduction of peripheral vascular resistance accompanied by an increase in cardiac output could not be inhibited by Practolol, a β_1 -selective blocker, while the increase in heart rate and shortening of preejection period were diminished, indicating at least in part the contribution of β_1 -stimulating effects of Nifedipine.

Van den Brand et al⁹⁾ also reported a significant increase in Vmax after administration of Nifedipine, suggesting the possibility that Nifedipine has a positive inotropic effect on the myocardium. Despite many experimental and clinical studies, the inotropic effect of this preparation has remained controversial.^{3), 10)–13)} Therefore, at present, a reflexogenic increase in heart rate is considered to play a principal role in the increase in cardiac output.

Since a marked reduction of the peripheral vascular resistance was observed along with a fall in the blood pressure, the mechanism of this preparation in lowering the blood pressure is considered primarily due to the peripheral vasodilatation. Similar results were observed in animal experiments,¹⁰⁾ in lesser degree in healthy subjects⁸⁾ and patients with angina pectoris.¹⁴⁾ These findings are in agreement with the observation reported by Murakami et al¹⁾ on patients with hypertension.

In anesthetized dogs, Vater et al¹³⁾ showed that Nifedipine had a marked vasodilating effect on systemic arteries in addition to the coronary arteries and suggested that its action is more prominent in large arteries in the trunk than in small arteries in the extremities. They also stated that the vasodilating effect of Nifedipine would be due to its inhibition of the adrenaline activity on the smooth muscle rather than its blocking effect on the receptor, since it inhibited the pressor elevation induced by intravenous injection of noradrenaline, angiotensin, or tyramine.

It has been known that Ca^{++} is an important ion to regulate the tonus of smooth muscle. A possible relationship between calcium metabolism and pathogenesis of hypertension was suggested by an observation that hypertension was often found among patients with hyperparathyroidism¹⁵⁾ and hypertension disappeared with normalization of calcium metabolism after surgical operation thereof.¹⁶⁾

When the myocyte is depolarized, availability of Ca^{++} increases to be combined with troponin, consequently inhibition of contraction is lifted. Then, actin and myosin act with each other leading to the contraction of the mus-

cle.¹⁷⁾ Ca^{++} involved in the contraction is assumed to be derived from following 2 processes; one released from the sarcoplasmic reticulum in the cell (bound Ca^{++}) and the other transported into the cell via the slow inward current (Ca^{++} influx).

According to Imai et al,¹⁸⁾ among Ca^{++} antagonists Nifedipine and verapamil inhibit the use of bound Ca^{++} and diltiazem and trimetazidine inhibit both bound Ca^{++} and Ca^{++} influx to suppress the contraction of smooth muscle.

From clinical observations, differences in their effects among Ca^{++} antagonists are noted, particularly in hypotensive effects. While Nifedipine exerts a pronounced hypotensive effect in a short time, diltiazem has a rather mild hypotensive effect by a long-term oral administration, especially in combination with thiazide diuretics.¹⁹⁾ However, it was reported that diltiazem showed a potent hypotensive effect in a short time as well as Nifedipine when it was administrated intravenously.²⁰⁾

Although it has been shown that Nifedipine acts on the arterial system and dilate it, its influences on the venous system have not been completely clarified. Mostbeck et al²¹⁾ reported from the study of whole body scanning with a gamma camera after intravenous injection of $^{99\text{m}}\text{Tc}$ -labelled human albumin, that no shift of the blood volume occurred from the limbs to the trunk after the administration of Nifedipine and stated that this preparation has no dilating effect on the capacitance vessels.

In this respect, this preparation differs from isosorbide dinitrate and sodium nitroprusside, but resembles the action of hydralazine and minoxidil.⁶⁾

The present study showed that left ventricular end-diastolic dimension remained unchanged after the administration of Nifedipine in the majority cases and a reduction of afterload may play an important role in the increase in ejection fraction. However, possibility of the positive inotropic effect of the agent could neither be confirmed nor excluded from the present study.

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