Case Reports

Effectiveness of Long-Acting Nifedipine in Pheochromocytoma

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SUMMARY

In the present study, we report a case of pheochromocytoma whose high blood pressure was well controlled by single-agent therapy with long-acting nifedipine, in spite of the failure of the combination of labetalol and prazosin in lowering blood pressure satisfactorily. A 48 year old female was first noted to have hypertension (160/100 mmHg) at 45 years of age. Hypertension was not controlled by conventional antihypertensive drugs. She was admitted to Fukui Prefectural Hospital in September, 1985. Her blood pressure on admission was 210/110 mmHg. Extraction of the left adrenal gland containing a pheochromocytoma (30×37×10 mm) was performed in November, 1985. Her hypertension and abnormally high plasma noradrenaline (NA) concentration (1,760 pg/ml, normal value 40–350 pg/ml) were sustained even after operation. Combination therapy with labetalol (400 mg/day) and prazosin (6 mg/day) was unsatisfactory, and the addition of long-acting nifedipine (40 mg/day) produced a marked decrease in blood pressure. Furthermore, single therapy with long-acting nifedipine was effective. No reduction of urinary NA excretion was observed in our patient during long-acting nifedipine therapy, suggesting that the decrease in blood pressure was not caused by suppression of NA release from pheochromocytoma tissue.

Additional Indexing Words:

Pheochromocytoma Calcium antagonist Nifedipine

LABETALOL, which has both alpha- and beta-adrenoreceptor blocking actions, and/or prazosin which is a postsynaptic alpha-adrenergic receptor blocker, have been used for the management of high blood pressure secondary to pheochromocytoma.¹⁾ Recently, Serfas et al reported that nifedipine, a calcium-channel blocker, controlled labile blood pressure in a case of pheochromocytoma, possibly by interfering with the release of noradrenaline (NA) from pheochromocytoma tissue.²⁾ In the present study, we

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Received for publication May 9, 1988.

Accepted March 10, 1989.

report a case of pheochromocytoma whose high blood pressure was well controlled by the use of long-acting nifedipine alone, in spite of the failure of the combination of labetalol and prazosin to lower blood pressure satisfactorily. Plasma concentrations and urinary excretion of NA and adrenaline (A) were extensively studied. The relationship between the effect of long-acting nifedipine on catecholamine secretion from pheochromocytoma and its effect on blood pressure is discussed.

CASE REPORT

A 48 year old female was first diagnosed as having hypertension (160/100 mmHg) when she visited her family doctor because of headache and easy fatigability at 45 years of age. Hypertension was not controlled by conventional antihypertensive drugs. She was admitted to Fukui Prefectural Hospital in September, 1985. Her blood pressure on admission was 210/110 mmHg. She did not complain of any symptoms suggestive of a hyperadrenergic state. Extensive investigation including abdominal computerized tomography (CT), angiography and determination of catecholamine concentrations in the peripheral vein, adrenal vein and urine, etc., confirmed the presence of a left adrenal pheochromocytoma. Extraction of the left adrenal gland containing a pheochromocytoma (30×37×10 mm) was performed in November, 1985. Her hypertension and abnormally high plasma NA concentration (1,760 pg/ml, normal value 40–350 pg/ml) were sustained even after surgery (Table I). Figure 1 shows the course of her blood pressure and pulse under various antihypertensive agents. In spite of removal of the left adrenal gland with the pheochromocytoma, her blood pressure remained high. Therefore, combination therapy with labetalol (400 mg/day) and prazosin (6 mg/day) was started. In April, 1986, long-acting nifedipine

Table I. Plasma Noradrenaline (NA) and Adrenaline (A) Concentration (pg/ml) and Urinary Excretion of Noradrenaline and Adrenaline (μg/day)

	Plasma NA	Plasma A	Urine NA	Urine A
Before the first operation	2950.0±963.7 (n=3)	80.3±25.2 (n=3)	667.7±60.3 (n=3)	35.6±5.9 (n=3)
After the first operation without medication	1435.0±115.0 (n=2)	55.0±35.4 (n=2)	302.0 (n=1)	34.4 (n=1)
During nifedipine single therapy	1040.0±280.0 (n=3)	50.0±11.5 (n=3)	328.0±37.6 (n=3)	29.0±16.7 (n=3)
After the second operation	140.0±11.5 (n=3)	10.0±0.0 (n=3)	71.4±5.2 (n=3)	13.9±3.3 (n=3)
Normal value	40–350	<20	29–120	1–23

mean±SE

Fig. 1. Clinical course of blood pressure (BP, ●—●) and heart rate (HR, ○—○) during treatment with various antihypertensive agents. Labetalol (400 mg/day), prazosin (6 mg/day) and long-acting nifedipine (40 mg/day) were administered orally.

(40 mg/day) was added since reduction of her blood pressure was not satisfactory. Addition of long-acting nifedipine produced a marked decrease in blood pressure from 180/90 mmHg to 140/80 mmHg. She was admitted to Fukui Medical School Hospital for closer examination in April, 1986. Her blood pressure on admission was 134/88 mmHg. We tried single-therapy with long-acting nifedipine (40 mg/day) to confirm the effect of long-acting nifedipine alone. Her blood pressure was well controlled by single-therapy nifedipine even after withdrawal of labetalol and prazosin. Laboratory data on admission (Table II) showed slight anemia, hyperglycemia, high plasma NA concentration (760 pg/ml) and high urinary NA excretion (304 μ g/day). ECG showed slight left ventricular hypertrophy without ischemic changes. Abdominal CT (Fig. 2) exhibited a nodule (30 $\times$ 23 mm) in the area of the left adrenal gland probably due to residual pheochromocy-

Table II. Laboratory Data on Admission to Fukui Medical School Hospital in April, 1986

WBC	5,500 / μ l	Urinalysis	Protein	(-)
RBC	3.86×10^6 / μ l		Glucose	($\pm$)
Hb	12.2 g/dl		Ketone	(-)
Ht	36.2%	FPG		142 mg/dl
Plt	392×10^3 / μ l	Hb A ₁		8.5%
Na	137 mEq/l	A _{1C}		6.6%
K	3.7 mEq/l	PRA		2.2 ng/ml/hr
Cl	100 mEq/l	Aldosterone		108.6 pg/ml
Ca	4.6 mEq/l	T ₃		1.0 ng/ml
P	3.4 mg/dl	T ₄		9.1 μ g/dl
BUN	11 mg/dl	TSH		3.5 μ U/ml
Cr	0.9 mg/dl	PTH-C		0.6 > ng/ml
T.P.	7.2 g/dl	Calcitonin		72 pg/ml
Alb	4.1 g/dl	AFP		5.0 > ng/ml
T-Bil	0.2 mg/dl	CEA		1.5 ng/ml
GOT	15 IU/l	Gastrin		79.2 pg/ml
GPT	34 IU/l	Plasma catecholamine		
LDH	317 IU/l	A		50 pg/ml
ALP	279 IU/l	NA		760 pg/ml
γ -GTP	39 IU/l	DA		200 > pg/ml
CPK	34 IU/l	Urine catecholamine		
Amylase	169 IU/l	A		26.3 μ g/day
CRP	(-)	NA		304 μ g/day
T-Chol	186 mg/dl	VMA		6.2 mg/day
TG	135 mg/dl	HVA		4.2 mg/day
HDL-Chol	40 mg/dl	Urine 17-KS		4.5 mg/day
		17-OHCS		4.9 mg/day

toma. Venous sampling data (Fig. 3) showed that concentrations of NA and A in the sample obtained from the left adrenal vein were 100,000 pg/ml and 6,100 pg/ml, respectively, values which were significantly higher than those in other veins. The left adrenal venogram (Fig. 3) exhibited hypervascular staining with neovascularization. The second operation performed in July, 1986, revealed residual pheochromocytoma pathologically, suggesting that the first operation failed in the complete removal of the pheochromocytoma. No antihypertensive drugs were necessary after the second operation. Table I shows the changes of plasma NA and A concentration and urinary excretion of NA and A during her clinical course. Reductions of urinary NA and A excretion were not observed in our patient during long-acting nifedipine therapy.

Fig. 2. Abdominal CT.

Fig. 3. Adrenal venogram (left) and concentrations of noradrenaline and adrenaline in various veins, including the adrenal vein (right).

DISCUSSION

It has been suggested that urinary NA and A excretion are more reliable markers of catecholamine secretion from pheochromocytoma because of the unstability of plasma NA and A concentrations. The lack of a reduction of urinary NA and A excretion observed in our patient during long-acting nifedipine therapy suggests that the decrease in blood pressure was not caused by suppression of NA and A release from pheochromocytoma tissue. It is controversial whether or not calcium antagonists suppress catecholamine secretion from pheochromocytoma tissue. Serfas et al²⁾ reported that nifedipine interfered with the release of noradrenaline from pheochromocytoma tissue, while Favre et al³⁾ reported that nifedipine appeared to control hypertension in pheochromocytoma without altering catecholamine levels, suggesting that calcium-channel blockade interferes with catecholamine's vascular action but not with tumoral catecholamine release. Furthermore, other calcium antagonists such as diltiazem⁴⁾ and verapamil⁵⁾ did not suppress catecholamine secretion. The data of the present case suggest that long-acting nifedipine was effective in reducing hypertension in this patient with pheochromocytoma without affecting NA and A secretion. It has been shown that nifedipine induces a substantial reduction in vascular responsiveness to NA.⁶⁾ Reduction of blood pressure by nifedipine observed in the present case might be caused partly by the effect of nifedipine on vascular smooth muscle to decrease total peripheral resistance. However, it is not clear why the antihypertensive effect of nifedipine in this case was greater than the combination of labetalol and prazosin. The results in our patient confirm the hypotensive effect of nifedipine on high blood pressure in patients with pheochromocytoma, but do not support the hypothesis of an inhibition by nifedipine of catecholamine secretion from pheochromocytoma *in vivo*. In order to elucidate the specific mechanism of hypotensive effects of nifedipine in patients with pheochromocytoma, further pharmacological studies are needed.

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