Postgraduate Medical Journal (December 1973) **49**, 908–913.

Treatment of severe hypertension and hypertensive emergencies with intravenous clonidine hydrochloride

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Summary

Eleven severely hypertensive patients, median age 54 years, were treated with intravenous (i.v.) clonidine hydrochloride (Catapres). In nine there were life-threatening complications: severe left ventricular failure (LVF), hypertensive encephalopathy, cerebral haemorrhage, dissecting aortic aneurysm, renal failure, and severe epistaxis. In two patients there was pronounced, but uncomplicated, elevation of blood pressure. 0·15 mg or 0·3 mg clonidine was given every 40 min with electrocardiographic (ECG) monitoring. The mean systolic and diastolic blood pressures in the eleven patients were respectively 266 and 165 mmHg before treatment falling to 165 and 109 mmHg after treatment ($P < 0·001$). The mean decrease in heart rate was 26 beats/min ($P < 0·001$). Doses of clonidine required for control ranged from 0·15 mg (one ampoule) to 0·9 mg (mean 0·56 mg), although one patient received a total of 0·9 mg without an adequate response. The presenting condition caused the eventual death of two patients. There were no serious side effects, except for one transient episode of sino-atrial heart block. It is concluded that clonidine is effective and safe in the treatment of hypertensive emergencies.

Introduction

Clonidine hydrochloride (Catapres) is an imidazoline derivative which lowers blood pressure when administered in microgram (μg) doses. (Conolly, 1969). To date, a number of publications have shown clonidine to be an effective oral treatment in mild, benign or moderate hypertension (Gifford, 1969; Kellett & Hamilton, 1970; MacDougall *et al.*, 1970), in severe hypertension (Raftos, 1969; MacDougall *et al.*, 1970) and hypertension in pregnancy (Turnbull & Ahmad, 1969; Johnston & Aickin, 1971). In other studies the drug has compared well with methyldopa in various clinical trials. Thus, Finnerty (1969) concluded that the fall in arterial pressure with chlorothalidone plus clonidine was slightly greater than with chlorothalidone and methyldopa. Conolly, Paterson & Dollery (1969) found close resemblance in the efficacy and side effects between clonidine and methyldopa. Amery *et al.* (1970) concluded that the diastolic morning blood pressure could be reduced to 95 mmHg or below in significantly more patients with clonidine than with methyldopa, but clonidine had more side effects. In a comparison with guanethidine, clonidine had the same or often better hypotensive effect (Hoobler & Sagastume, 1969). Thiazide diuretics enhance clonidine's hypotensive effect (Onesti *et al.*, 1969; Gifford, 1969). Intravenous clonidine has been used in haemodynamic studies in normotensive subjects and patients with uncomplicated hypertension (Barnett & Cantor, 1968; Finnerty, 1969; Muir, Burton & Lawrie, 1969; McRaven *et al.*, 1971), and in the treatment of hypertensive emergencies, where it proved very effective and favourably comparable with reserpine, guanethidine, hydralazine and alpha-methyldopa, since it caused the greatest decrease in blood pressure 1 and 2 hr after drug administration (Onesti *et al.*, 1971). However, in their paper Onesti *et al.*, gave no details regarding the nature, clinical condition of the patients and the outcome of the emergencies treated. Since no ideal drug for the treatment of hypertensive crises yet exists we thought that further evaluation of i.v. clonidine might be useful. We report here our experience with i.v. clonidine in patients with severe hypertension and life-threatening hypertensive emergencies.

Patients and methods

Five male and six female patients who were considered to require urgent reduction of blood pressure were treated with i.v. clonidine using a standardized regime (see below). Ages ranged from 25 to 70 years, median 54 years. Six had essential and five renal hypertension of duration 1 to 12 years, this being unknown in two. Three had received no previous treatment for hypertension. In two there was no frank hypertensive crisis but they were in-

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TABLE 1. Clinical details

Case no.	Sex	Age	Type of hypertension	Duration (years)	Previous treatment	BP before treatment (mmHg)	Hypertensive emergency	Fundi grade	LV hypertrophy	
									ECG	X-ray
1	F	46	Essential	1	No	270/180	—	II	+	+
2	F	64	Essential	12	Yes	290/180	Cerebral haemorrhage. Mild LVF	III–IV	+++	ND
3	M	47	Essential	3	Yes	280/180	Encephalopathy Mild LVF	II–III	+++	+++
4	F	24	Renal	9	Yes	240/150	—	II	+	++
5	M	70	Essential	16	Yes	200/150	Severe epistaxis	II	++	++
6	F	70	Essential, diabetes mellitus	12	Yes	270/160	Encephalopathy	II–III	+++	++
7	M	56	Renal	7	Yes	290/170	Severe LVF	II–III	+++	++
8	M	48	Essential	Unknown	No	280/170	Dissecting aortic aneurysm	I	++	?
9	F	54	Renal	Unknown	No	310/170	Severe LVF, renal failure	II	++	+
10	M	69	Essential	6	Yes	250/140	Encephalopathy	II	++	+
11	F	34	Renal	7	Yes	250/150	Encephalopathy	III–IV	++	+

+, slight; ++, moderate; +++, marked; ND, not done.

cluded because of very high diastolic pressure associated with severe headache. The blood pressure on admission, nature of hypertensive emergency, clinical and other findings are given in Tables 1 and 2.

As soon as the diagnosis and decision to treat urgently was made, the level of blood pressure recording was confirmed by two independent observers. A chest radiograph was obtained and blood taken for serum creatinine, urea, electrolytes and routine haematology. A 12-lead ECG was recorded initially and monitored throughout treatment.

All patients had a slow continuous i.v. drip of 5% dextrose, nine received 0·15 mg (one ampoule) of clonidine and two 0·3 mg, via the injection rubber of the giving set, every 40 min until the diastolic blood pressure had fallen to 120 mmHg or below, a level decided by us to represent satisfactory control in these circumstances. As experience was gained, however, and no serious unwanted effects were observed, some patients received additional injections. Oral clonidine 0·2 mg four times daily was started when the blood pressure was controlled and the i.v. treatment discontinued.

TABLE 2. Main signs and symptoms

	No. observed
Severe headache	4
Hemi- or monoplegia	3
Aphasia or dysphasia	4
Unconscious	2
Orthopnoea—cyanosis	2
Convulsions	3
Oliguria—azotaemia	1
Epistaxis	1

Blood pressures were recorded before and every 10 min during treatment by one of us (A.P.N.) using a mercury sphygmomanometer (Pickering, 1968). By agreement, the first Korotkow sound corresponded to the systolic blood pressure and the disappearance of sound to the diastolic. The heart rate was taken from the ECG at the time of blood pressure measurement. Conscious patients were tilted to the 45° head-up position. A resuscitation trolley with the appropriate drugs, defibrillator and pacemaker were at hand. No other drugs were given during treatment with the exception of three patients who received frusemide and digoxin and one phenytoin.

Fluid balance charts were carefully kept and serum creatinine and blood urea were estimated shortly after treatment.

Results

Blood pressure and heart rate changes

In all but one patient the blood pressure fell to 120 mmHg diastolic or below (Table 3). The mean systolic and diastolic pressures before treatment were 266 and 165 mmHg respectively falling with treatment to 165 systolic ($t=10{\cdot}43$, $P<0{\cdot}001$) and 109 diastolic ($t=11{\cdot}00$, $P<0{\cdot}001$). These changes are highly significant. Figure 1 shows the mean response of blood pressure and heart rate after injection of 0·15 mg clonidine at 40 min intervals and Fig. 2 the individual overall responses. The reduction in blood pressure was smooth in all cases without sudden pressure variations and there were no hypotensive episodes, even when injections of 0·3 mg

TABLE 3. Blood pressures before and during treatment with clonidine i.v.

Case no.	Before clonidine	Minutes from start of treatment				Total i.v. dose (mg)	Outcome
		40	80	120	160		
1	270/180	230/170	190/155	170/120	OT	0·45	Controlled. Survived
2	290/180	150/100	OT	OT	OT	0·15	Controlled. Died
3	280/180	260/180	220/160	210/145	200/150	0·90	Not controlled. Survived
4	240/150	190/160	165/120	140/100	OT	0·45	Controlled. Survived
5	200/150	170/130	165/110	140/90	OT	0·45	Controlled. Survived
6	270/160	210/120	160/90	OT	OT	0·30	Controlled. Survived
7	290/170	270/170	210/150	190/130	170/110	0·60	Controlled. Survived
8	280/170	250/160	200/130	170/110	OT	0·45	Controlled. Died
9	310/190	260/180	220/150	180/130	160/115	0·60	*Controlled. Survived
10	250/140	230/130	250/140	210/110	OT	0·90	†Controlled. Survived
11	250/150	180/140	150/120	150/110	OT	0·90	†Controlled. Survived

*Diuretic+digoxin in addition. † Each injection 0·3 mg. OT, start of oral treatment at this time.

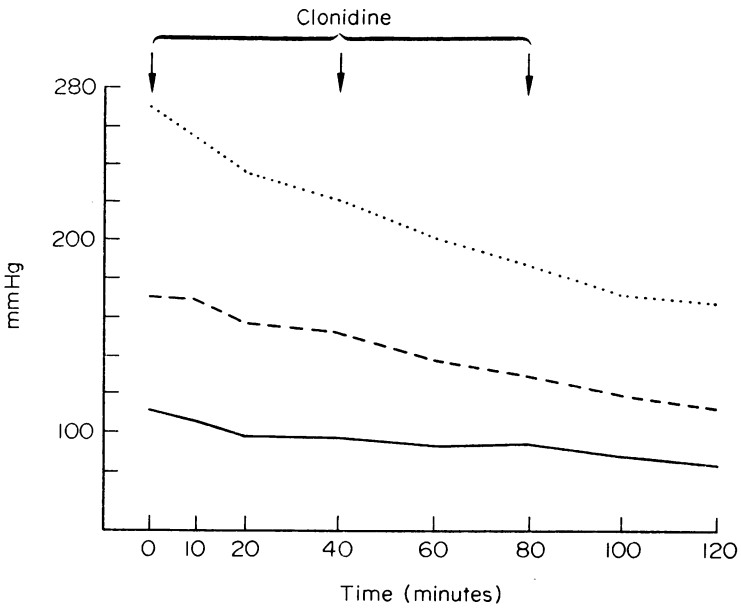

FIG. 1. Changes in mean systolic (· · · · · ·) and diastolic (- - - -) blood pressures and heart rate (——) during treatment.

were used. There was a greater fall in systolic than diastolic pressure, particularly during the early stages. Heart rate fell initially with less change after subsequent injections (Fig. 3), the overall mean reduction being 26 beats/min ($t=8{\cdot}64$, $P<0{\cdot}001$). In two patients 0·15 mg was adequate to achieve a diastolic pressure of 120 mmHg, though further injections were required in the other patients (Tables 3 and 4, Fig. 4). With the exception of one patient who did not reach the desired diastolic level after 0·9 mg, the mean dose to achieve this level was 0·56 mg.

Outcome and follow-up

The reduction of blood pressure brought symptomatic improvement in most of the patients. Thus headaches became less severe in all, speech improved in three, and consciousness in one. Convulsions ceased in two. The third was controlled by phenytoin. In case 5, nasal bleeding ceased when the diastolic pressure fell to 120 mmHg. Of the eleven patients, two died despite adequate control of blood pressure. Case 2 was admitted with a massive cerebral haemorrhage and died 7 hr later, the diagnosis being confirmed at necropsy. The other patient (case 8)

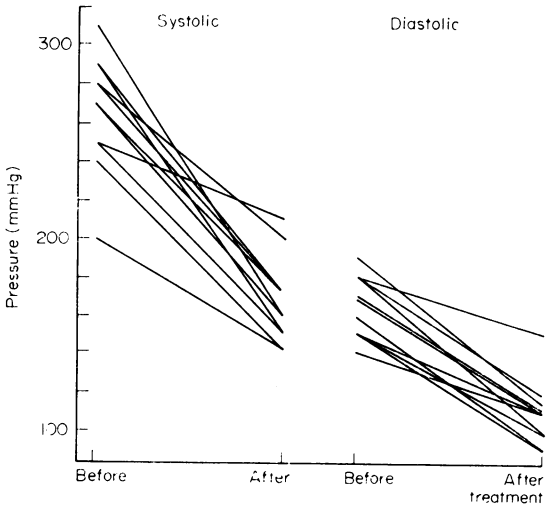

FIG. 2. Systolic and diastolic blood pressures before and after treatment with i.v. clonidine.

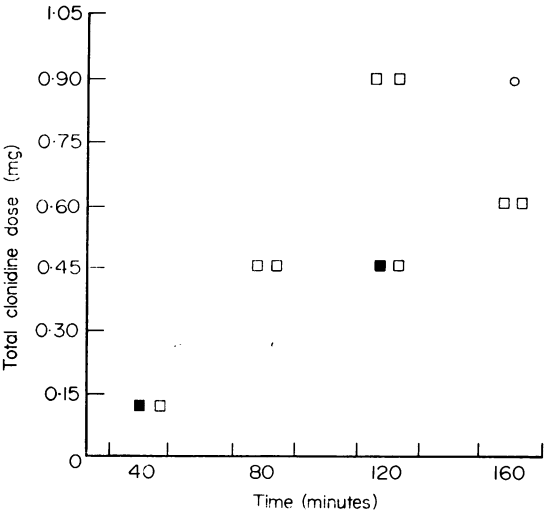

FIG. 4. Dose of clonidine and time required for control of blood pressure in the eleven patients. □, controlled, survived; ■, controlled, died; O, not controlled, survived.

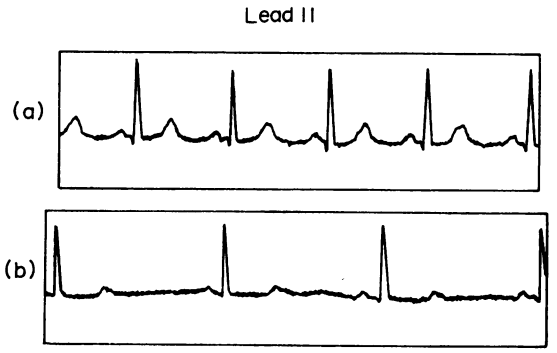

FIG. 3. Case 1. Blood pressure and heart rate before (a) and after (b) i.v. clonidine. a, BP 270/180 mmHg; b, BP 165/120 mmHg.

TABLE 4. Dose of clonidine and time required for control of blood pressure in the eleven patients

Clonidine total dose (mg)	No. of patients			Time (min)
	Total	Controlled	Not controlled	
0·15	2	2*	9	40
		2		80
0·45	4	2*	5	120
0·60	2	3	3	160
0·90	3	2	1	120
Total	11	10	1	—

* One died.

had a dissecting aortic aneurysm (Fig. 5) and died suddenly on the third day after admission. At necropsy, a tear 1 cm long was found in the aortic inner wall 3 cm above the aortic valve, with dissection extending to the common iliac arteries. One patient in renal failure (case 9) needed haemodialysis for 3 days, and one (case 7) underwent left nephrectomy 2 weeks after admission. Case 3 who became resistant to clonidine and pentolinium was eventually controlled using diazoxide.

Side effects

During the i.v. treatment no serious side effects were observed (Table 5) and most of them were transient. One patient developed a transient sino-atrial heart block. Serial ECGs showed spontaneous reversion to normal sinus rhythm. During the oral treatment drowsiness and dry mouth were common during the first days of treatment.

Fluid balance

Eight patients had normal fluid balance, two had positive fluid balance due to left ventricular failure which was treated with frusemide, one patient developed positive fluid balance due to acute ventricular and renal failure which were treated with haemodialysis.

Renal function

The pre-treatment and shortly after treatment values for serum creatinine and blood urea did not differ significantly (Table 6).

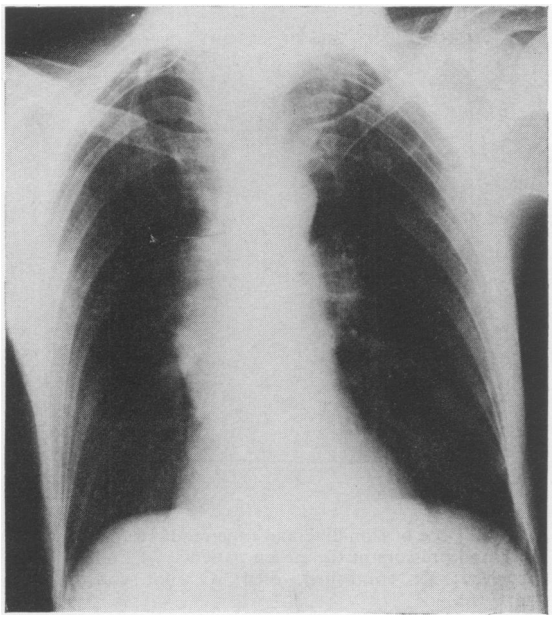

FIG. 5. Case 8. Dissecting aortic aneurysm confirmed by necropsy.

TABLE 5. Side effects during the i.v. treatment

	No. observed
Sinus arrhythmia	3
Sinoatrial heart block (transient)	1
Dizziness	2
Sleepiness	2
Tiredness	2
Tremor	1
Over-breathing	1

TABLE 6. Renal function tests before and after treatment

	Before		After	
Case no.	Serum creatinine (mg%)	Blood urea (mg%)	Serum creatinine* (mg%)	Blood urea† (mg%)
1	0·9	30	1·1	32
2	0·8	40	ND	ND
3‡	1·6	46	1·2	32
4	1·0	28	1·2	40
5	0·8	34	1·0	38
6	1·2	46	1·2	40
7‡	1·4	60	1·1	42
8	1·3	50	ND	46
9‡	2·6	140	1·4§	60§
10	0·9	40	1·1	36
11	1·4	48	1·0	36
Mean	1·26	51·1	1·14	40·2

* Serum creatinine: mean difference = −12·0, t = 1·49, not significant.
ND, not done.
† Blood urea: mean difference = −0·17, t = 1·07, not significant
‡ Patient received frusemide.
§ Patient had haemodialysis (see text).

Discussion

This series, though small, showed intravenous clonidine to be very effective in reducing both systolic and diastolic blood pressures in all but one patient. Control was obtained in eight patients within 2 hr, and within 2 hr and 40 min in the remaining two. Although the desired speed of pressure reduction in emergencies is still controversial (Vaamonde, David & Palmer, 1971) larger and more frequent injections may be more effective. Considering the range of hypertensive emergencies treated (encephalopathy, LVF, renal failure and severe epistaxis), the potency, speed of action, contra-indications and side effects of the currently available hypotensive drugs, clonidine appears to be superior to reserpine, methyldopa, hydralazine and guanethidine, and probably equal to pentolinium. In the doses given, however, when compared with trimetaphan, sodium nitroprusside and diazoxide, clonidine appeared to be inferior in speed of action and potency but nevertheless had less serious side effects (Breslin, 1969; Vaamonde *et al.*, 1971). Despite good control of blood pressure, the two deaths were inevitable, since both severe cerebral haemorrhage and dissecting aneurysm carry a high mortality.

In no case was a rise in blood pressure seen when clonidine was first given (Finnerty, 1969; Muir *et al.* 1969; McRaven *et al.*, 1971) nor was there noticeable impairment of renal function. Side effects were not troublesome. The transient sino-atrial heart block in one patient may be due to an increase in vagal tone, such changes in vagal tone have been demonstrated in animals by Robson & Kaplan (1969) and may contribute to the bradycardia seen in a proportion of patients (Muir *et al.*, 1969; McRaven *et al.*, 1971). Because of this, continuous ECG monitoring is advisable during the i.v. treatment.

The mode of action of clonidine is still uncertain but it can be divided into central, associated with reduced sympathetic tone (Schmitt *et al.*, 1967) together with increased vagal tone (Robson & Kaplan, 1969; Kobinger & Walland, 1971), and peripheral, characterized by a reduction in the response of vascular smooth muscle to stimuli (Zaimis & Hanington, 1969). The hypotension following i.v. clonidine is predominantly due to reduction in cardiac output without a corresponding rise in peripheral resistance (Muir *et al.*, 1969; Onesti *et al.*, 1971).

We conclude that clonidine is a safe and effective alternative drug for the treatment of severe hypertension and hypertensive emergencies. For the successful treatment of some hypertensive emergencies, however, combination with diuretics, digoxin, anti-convulsants, dialysis or other measures may still be required.

Acknowledgments

We are very grateful to all consultants who allowed us to treat patients in their care, to Dr J. W. Bell for stimulating discussions, to Mrs P. Pollard for statistical help, and to Miss E. Mooney for typing the manuscript and drawing the figures.

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Postgrad Med J 1973 49: 908-913
doi: 10.1136/pgmj.49.578.908