Clonidine in the Management of Uncontrolled Hypertension

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SUMMARY

The antihypertensive effect of clonidine hydrochloride (Catapres) was investigated in patients with uncontrolled hypertension. In 25 ambulant outpatients a double-blind crossover trial was performed by adding clonidine or its placebo at random in succession for a month, to existing antihypertensive regimens. A second group of patients with severe hypertension and renal failure was investigated in a single-blind fashion. In the double-blind study, 21 patients completed the trial. Sitting blood pressures were reduced from $\frac{208\pm6}{122\pm3,7}$ to $\frac{162\pm5,0}{98\pm2,5}$ mmHg ($P<0,001$); standing blood pressures from $\frac{198\pm7,2}{121\pm3,2}$ to $\frac{153\pm4,3}{97\pm2,7}$ mmHg ($P<0,001$). There was no increase in postural effect. Placebo treatment caused only a small decrease in systolic pressures, but no decrease in diastolic pressures. Forty-four per cent of patients had bothersome sedation and 60% complained of a dry mouth. In the single-blind study, the mean follow-up period for 11 patients was 14,6 months. During this time with clonidine included in their regimens, renal function deteriorated in 2 patients, improved in 5 and remained unchanged in 4. The drug exerted a powerful antihypertensive effect in the supine position in many of these patients. Clonidine is a useful antihypertensive drug, particularly in those patients with compromised renal function.

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Treatment of patients with mild to moderate hypertension with a diuretic and one of a number of modern antihypertensive drugs causes a dramatic reduction in the morbidity and mortality associated with hypertensive disease.[1,2] Such simple treatment regimens are associated with a negligible incidence of side-effects attributable to the drugs, since relatively small amounts are used. On the other hand, the management of severe and malignant forms of hypertension often presents a formidable challenge. Unless actively and effectively treated, such patients often succumb to complications of their disease within a few months. Their therapy is often complicated by the fact that several drugs have to be used in large amounts and the side-effects of the drugs used may not only add significant problems, but may adversely affect the prognosis of the patient. The search for more satisfactory drugs to use in these patients, therefore, has to continue.

The purpose of this study was to evaluate by double-blind trial the use of the new antihypertensive drug, clonidine hydrochloride, in patients with moderate to severe hypertension, who were either not responding satisfactorily to their existing treatment regimens, or in whom side-effects of other drugs impaired their effective control. A single-blind study was also conducted in a separate group of patients with malignant hypertension or hypertension with significant renal failure, with special reference to whether the drug acted effectively while these patients were confined to bed.

PATIENTS AND METHODS

Double-Blind Crossover Group

Twenty-five ambulant hypertensive patients attending the Groote Schuur Hospital Hypertension Clinic were selected for the reason that their blood pressures were

TABLE I. DETAILS OF PATIENTS SELECTED FOR DOUBLE-BLIND TRIAL

Sex	Age	Admission BP	Fundi (K - W grade)	Trial entry BP	Daily dose of medications	Time on existing regimen (mo.)
F	68	290/130	II	230/110	A 1 500; D 2	6
M	54	180/120	II	190/125	A 1 500; D 2	3
F	50	260/140	III	250/160	A 3 000; G 20; D 2	3
M	49	300/170	IV	250/160	G 100; R 150; D 2	2
F	43	200/120	II	160/110	R 150; S 50; D 2	6
F	41	200/120	II	210/130	A 3 000; R 150; D 2	4
F	62	220/130	III	220/130	A 3 000; G 100; D 2	4
M	50	230/130	II	170/110	R 150; D 2	2
M	48	210/130	II	210/130	A 2 000; S 50; D 2	2
F	44	260/160	II	260/160	G 100; R 150; S 50; D 2	3
F	64	220/140	II	200/120	G 50; R 150; D 2	2
M	60	180/140	II	220/130	A 2 000; G 200; S 100	4
F	58	260/140	II	230/120	A 2 000; G 150; D 3	3
F	56	275/160	II	230/130	G 50; S 50; Db 180	3
F	42	230/180	III	190/130	A 2 000; S 50	2
F	66	270/130	II	210/120	A 2 000; D 2	6
F	68	220/120	II	200/100	A 1 500; 2 D	3
M	54	180/120	II	190/125	A 1 500; D 1	2
M	44	240/130	III	180/110	A 2 000; G 100; P 240; D 1	8
F	43	230/140	III	190/90	A 1 500; R 150; D 3	12
F	55	250/140	II	230/130	R 150; P 240; D 3	9
F	53	230/140	II	240/150	R 150; S 50; D 2	18
F	34	230/130	III	220/130	G 30; S 50; D 2	6
F	58	250/120	II	250/120	R 100; D 2	2
M	57	180/120	II	180/120	A 2 000; D 1	3

Medications: A = alphamethyldopa dose in mg/day; P = propranolol in mg/day; G = guanethidine dose in mg/day; S = spironolactone in mg/day; R = rauwolfia serpentina in mg/day; D = thiazide diuretic in tablets/day; Db = debrisoquine in mg/day.

inadequately controlled on large doses of several other antihypertensive drugs, or reasonable control was obtained with existing regimens but at the price of significant side-effects.

The details of the patients, including their blood pressures on first referral to the clinic, fundoscopic grading and blood pressures on existing antihypertensive regimens at the time of admission into the clonidine trial, are indicated in Table I. The daily amounts of their antihypertensive drugs are shown as well as the duration of treatment on these drugs.

Informed consent was obtained from all patients. Since patients with severe hypertension were selected, a protocol providing for *addition* of either clonidine or its matching placebo was chosen, rather than a protocol whereby current medicines were discontinued and *replaced* by either active drug or placebo. Clonidine or placebo was added at random, 1 tablet *t.i.d.* for a period of one month, after which alternative coded tablets were substituted without the knowledge of the patient. Each patient, therefore, received both clonidine and placebo for one month with a random allocation of either clonidine or placebo during the first of the two months. At the start and end of the two-month period electrolyte values, urea, creatinine and an SMA-12 channel screen including serum proteins, uric acid and serum enzymes were obtained.

At each visit, sitting and standing blood pressures were recorded without any alteration in the Clinic routine for the patient. The patients were asked whether they noticed anything different while on the tablets. Leading questions about side-effects were avoided.

The results were analysed by an analysis of variance, using an Olivetti Programma P203 computer. A P value of less than 0,05 was regarded as indicating significant changes.

Single-Blind Group

In this group were included patients with severe hypertension and concomitant renal failure who were confined to bed because of the severity of their hypertension. Selection of patients was on referral to the Hypertension Service. Only in one patient was a double-blind addition trial attempted, but this was ceased when a hypertensive response was noted on switching from clonidine to placebo tablets. (This is shown in Fig. 1.)

In a second group of patients with significant renal failure, clonidine was added to their existing antihypertensive regimen and the patients followed up as outpatients in the Hypertension Clinic. They were seen every month or more frequently, and had frequent estimations of blood chemistry determinations. The details of these patients are shown in Table II.

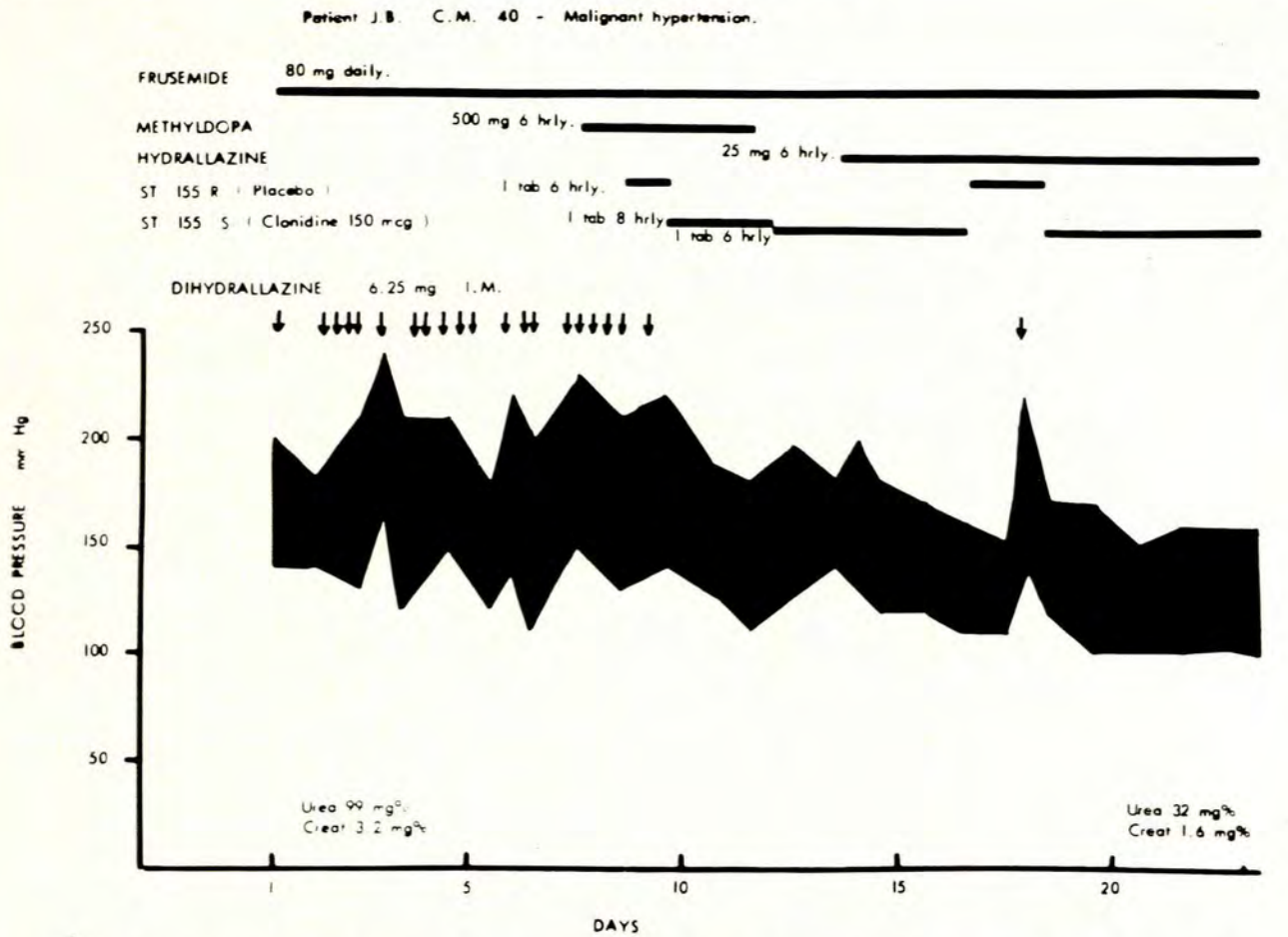

Fig. 1. The supine blood pressure responses of a patient during addition of clonidine hydrochloride, 150 μg every 8 hours at first, and then 150 μg every 6 hours. The substitution of clonidine with its placebo is followed by a rapid, severe rise in blood pressure. This was the only patient in this group who received placebo therapy.

TABLE II. PATIENTS WITH MILD RENAL FAILURE WHO ENTERED THE DOUBLE-BLIND TRIAL

On entry into trial					On completion of trial					
Urea (mg/100 ml)	Creat. (mg/100 ml)	Serum Na^+ (mEq/L)	Serum K (mEq/L)	BP (mmHg)	Urea (mg/100 ml)	Creat. (mg/100 ml)	Serum Na^+ (mEq/L)	Serum K (mEq/L)	BP (mmHg)	Diagnosis
52	1,4	141	3,6	230/135	50	1,2	135	4,6	200/110	Benign nephrosclerosis
91	3,4	139	4,5	200/120	78	3,0	141	4,2	160/90	Malignant hypertension
72	2,7	140	5,1	160/100	110	5,8	140	3,9	150/90	Chronic pyelonephritis
41	2,0	142	3,1	170/110	47	1,1	140	3,5	160/90	Benign nephrosclerosis
70	2,8	138	4,7	230/150	64	1,7	137	2,7	160/115	Malignant hypertension
66	2,4	143	4,8	160/110	37	1,1	142	4,2	140/100	Malignant hypertension
96	3,0	140	4,5	210/110	98	2,2	142	5,3	150/90	Chronic glomerulonephritis

RESULTS

Ambulant Outpatients; Double-Blind Crossover Group

Eleven patients had active principle added to their medications during the first month, while 14 patients received placebo first, followed by active principle during the second month. Four of the 25 patients who were admitted to the trial developed intolerable sedation on active principle and withdrew from the trial. The blood pressure responses of the remaining 21 patients are shown in Fig. 2. A lowering of diastolic pressure by more than

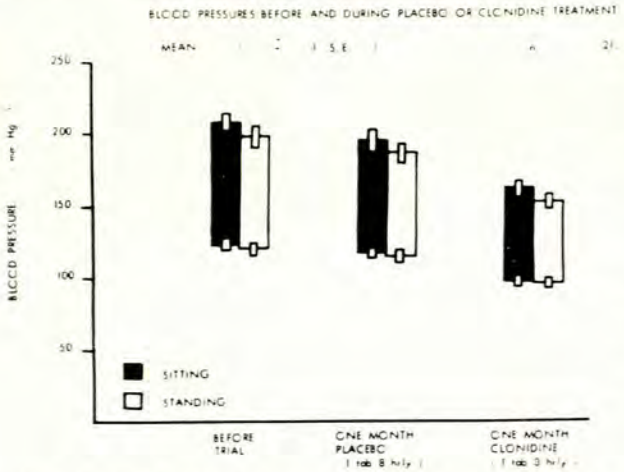

Fig. 2. Mean blood pressure responses in sitting and standing positions before entering into the trial, at the end of one month of placebo addition to their therapy, and after one month of clonidine addition.

20 mmHg was obtained in 18 patients, while diastolic pressures below 100 mmHg were obtained in 13 patients. The mean sitting blood pressures (± 1 SEM) on entry into the trial were $\frac{208 \pm 6,0}{122 \pm 3,7}$ mmHg, with the mean upright blood pressure $\frac{198 \pm 7,2}{121 \pm 3,2}$ mmHg. There was no change in either the sitting or standing diastolic pressures during the placebo period. A significant reduction in sitting and standing systolic pressures occurred to 196±6,4 mmHg and 187±5,2 respectively ($P<0,5$ in both instances). This finding emphasises the necessity for double-blind studies in hypertension.

After addition of 450 μg active principle daily for a month, the sitting blood pressures were $\frac{162 \pm 5,0}{98 \pm 2,5}$ mmHg; upright blood pressures $\frac{153 \pm 4,3}{97 \pm 2,7}$ mmHg. Statistical analysis revealed a significant reduction at the 1% level in each instance. There was no significant increase in postural response caused by the drug. Clonidine therefore caused a highly significant reduction in both systolic and diastolic pressures in both sitting and standing postures but had no postural effect in itself. A striking observation was the slowing of the pulse rate which occurred in those patients with the most marked reduction in blood pressures.

The incidence of side-effects was high. Four patients withdrew because of intolerable sedation. Forty-two per cent of the patients who completed the trial had bothersome sedation, while 66% complained of a dry mouth. Most patients felt these side-effects improved as the month of treatment passed. In those patients who entered the trial with normal haematological values and normal serum chemistry, no changes in these measurements were seen. The serum biochemical changes in those patients who entered the trial with abnormal renal function, are shown in Table II. Renal function remained unaltered in one patient, deteriorated in one patient, and improved in 5 patients over the period of one month by the criteria of serum urea and creatinine values. The patient who deteriorated died 8 months later from intractable renal failure.

Single-Blind Group with Severe Hypertension

Eleven patients were selected for this study. The details of these patients are given in Table III. Seven of these patients had malignant hypertension at the time of entry or immediately before referral; one had severe hypertensive disease with renal impairment but only grade II retinopathy. One patient had chronic glomerulonephritis diagnosed on the basis of bilaterally small kidneys with normal calyceal patterns on IVP, while two patients had chronic pyelonephritis diagnosed on the basis of irregularly-contracted kidneys. The duration of treatment with clonidine, the daily dose of this and the other drugs received by these patients, are included in this Table. The average blood pressure readings during the last 3 visits to the Clinic are indicated, and the serum urea and creatinine values at their last Clinic visit at the time of final assessment, June-August 1973, are included.

There was a satisfactory outcome in 10 of these patients with a mean follow-up period of 14,6 months, although normal blood pressures were obtained in only 3 patients. Renal function clearly deteriorated in 2 patients, was clearly improved in 5 patients, and remained unchanged in 4. Particularly notable was the return to normal function in 2 patients who had unequivocal malignant hypertension at the time of their entry into the trial. No patient was managed on clonidine alone.

Five of these patients were studied initially while confined to bed. The blood pressure responses of 2 are shown in Figs 1 and 3 respectively. In Fig. 1 the supine blood pressures of one of the patients are shown. This was the only patient in whom a double-blind study was attempted. The rapid rebound of blood pressure on replacement of active principle with placebo is demonstrated. This phenomenon was considered potentially dangerous in these patients, and thereafter the study was conducted in single-blind fashion. The response of another patient is indicated in Fig. 3. All blood pressures were recorded in the supine posture. This patient has returned to normal function, and is at work with a normal blood pressure on maintenance therapy with 225 μg clonidine, 50 mg hydrallazine and 1 Aldazide tablet daily.

TABLE III. PATIENTS, WITH FOLLOW-UP DATA, WHO WERE TREATED WITH CLONIDINE IN SINGLE-BLIND FASHION

			On starting clonidine					Daily dose of clonidine (μg)	At end of follow-up				
Age	Sex	Race	Blood pressure (mmHg)	Fundi	Urea (mg/100 ml)	Creat. (mg/100 ml)	Diagnosis		Duration (mo.)	BP (mmHg)	Urea (mg/100 ml)	Creat. (mg/100 ml)	Other drugs (mg/day)
47	M	C	240/120	III	74	4,5	Malignant hypertension	2 400	20	180/115	113	5,1	A 3 000; R 150; H 200; P 160
43	F	C	200/110	II	52	2,5	Benign nephrosclerosis	1 500	18	185/110	50	1,1	R 150; P 160; D 2
42	F	C	230/150	III	84	1,4	Malignant hypertension	1 500	20	150/105	70	1,8	A 2 000; D 2;
38	M	C	220/135	III	64	1,8	Malignant hypertension	1 200	21	170/110	37	1,1	G 25; P 80; D2
30	F	C	190/120	III	99	2,7	Malignant hypertension	600	24	130/100	46	0,6	P 80; D 1
46	M	B	230/130	IV	112	4,4	Malignant hypertension	600	9	200/110	154	7,9	R150; G 20; D 2; P 80
43	F	C	210/110	III	78	2,2	Chronic pyelonephritis	1 200	9	150/90	120	2,1	A 2 000; R 150; H 200; D 2
26	M	C	240/180	IV	30	1,7	Malignant hypertension	900	14	130/80	29	0,9	H 200; D 2
39	M	C	180/130	III	87	3,7	Chronic pyelonephritis	1 200	7	170/105	68	2,3	R 150; D 2
44	M	C	190/130	III	53	2,1	Chronic glomerulonephritis	900	6	170/100	43	2,1	A 2 000
38	F	C	190/110	III	55	1,5	Malignant hypertension	450	13	160/110	65	1,6	A 2 000; D 2

A = alphamethyldopa with daily dose in mg; P = propranolol with daily dose in mg; R = rauwolfia serpentina with daily dose in mg; G = guanethidine with daily dose in mg; H = hydrallazine with daily dose in mg; D = thiazide diuretic with daily dose in tablets.

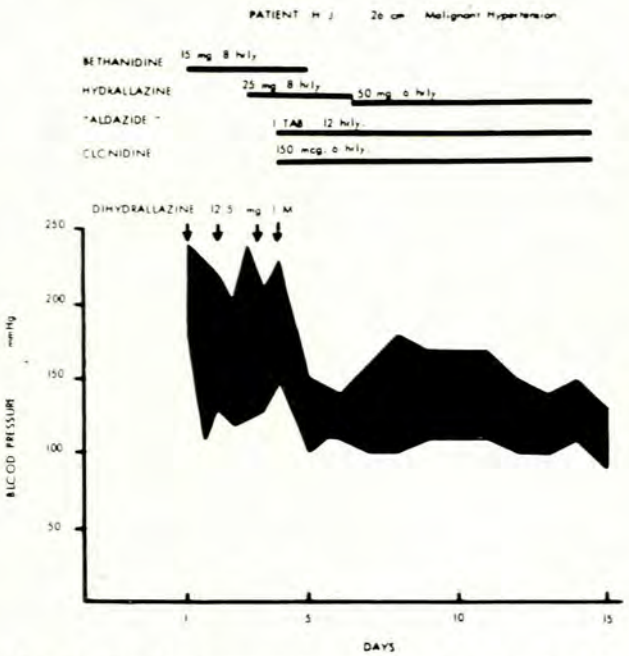

Fig. 3. The blood pressure response of a patient with malignant hypertension before and after addition of 150 μg clonidine hydrochloride every 6 hours. All readings are in the supine posture.

Several of these patients complained of sedation. It was felt that this was in fact an advantage in those patients confined to bed.

DISCUSSION

Mechanism of Action

Clonidine hydrochloride is an imidazole derivative with an apparently unique mode of action. This drug, active in μg quantities, acts in 2 ways:[3]

Central action: It is a central sedative which acts at the vasomotor centre to modify afferent impulses causing a reduced sympathetic and increased parasympathetic outflow. The sympathetic reflexes are maintained intact. The reduction in blood pressure is a function of the decrease both in pulse rate and in peripheral resistance.[4]

Peripheral action: At a vascular smooth muscle level,[5] this takes a longer time to develop. The action of this drug in alleviating the frequency and severity of migraine attacks in some patients is collateral evidence of this.[6]

It has also been postulated that the drug may act as a β-adrenergic blocking agent, since the heart is slowed and the actions of clonidine are antagonised by α-adrenergic blocking drugs.[7] Animal studies have failed to show an action in reducing myocardial contractility.[8]

In patients advantages of clonidine hydrochloride are the absence of a postural effect and its potent action in the supine state. The use of large doses of sympathetic ganglion blocking drugs with the attendant danger of

postural hypotension can, therefore, be avoided. The potent action in the supine posture coupled with the lack of an effect on sympathetic reflexes, makes the drug a suitable agent for use in patients due for anaesthesia. The relatively short action permits rapid adjustment of dosage, but necessitates a 3- or 4-times-a-day dosage schedule.

In patients with severe hypertension, the extent and progression of the concomitant renal failure often determines the prognosis of the patient. Conversely, in this group of patients, the control of the blood pressure is the most important factor in determining the outcome of the renal failure. The use of drugs that diminish renal blood flow, e.g. guanethidine, bethanidine, reserpine and the diuretics, should therefore be avoided. The only drugs known not to reduce renal blood flow are hydrallazine, alphamethyldopa and the β-adrenergic blocking agents. Onesti *et al.*[4] have demonstrated that clonidine hydrochloride, while antihypertensive, does not cause a diminution of renal blood flow. The present study confirms these observations at a clinical level. Although not controlled for the reasons discussed, the outcome of the majority of patients over a mean follow-up period of 14 months, was very gratifying in a disease with a natural history of less than 6 months, if left untreated. These results are supported by the observations published recently by Raftos *et al.*[9] who reported on 39 patients treated for more than 2 years with good results in 60%. The value of and freedom from side-effects on long-term treatment with clonidine alone, or in combination with a diuretic, have recently also been recorded by Mroczek *et al.*[10]

Current practice in the Hypertension Clinic at Groote Schuur Hospital is therefore to place all patients with hypertension and renal failure on a combination of clonidine, hydrallazine and a β-blocking drug or alphamethyldopa with minimal use of diuretics.

Clonidine has been shown to cause a mild degree of sodium retention[11] and therefore is best used with a diuretic. Since the drug does not cause reduction in splanchnic blood flow it is recommended by some authors for use in hypertension during pregnancy.[12] It appears to have no teratogenic effect and some authors feel that it is the drug of choice in the management of hypertensive crises in pregnancy.[13]

The high incidence of bothersome side-effects (sedation and dry mouth) was offset by the impressive absence of serious side-effects, even with administration of doses up to 2 400 μg daily for over a year. The recent publication by Mroczek *et al.*[10] reported similar findings. The drug appears, therefore, to be relatively safe and has a low incidence of interaction with other drugs. The diminution of the antihypertensive action of clonidine by a tricyclic antidepressant desipramine, has recently been documented.[14]

Current practice in our Clinic is to commence with a smaller dose, 75 μg *t.i.d.*, with increment of 75 μg per day only. This appears to decrease the severity of the side-effects until patients adapt to and tolerate the sedation and dry mouth.

The hypertensive response on withdrawal of clonidine reported in this study, has been documented by others.[15,16] It appears to occur mostly in severely hypertensive patients. These patients are often on other drugs as well, and these may serve to diminish this potentially serious side-effect of clonidine. Clinically it appears of little importance, since with widespread use of the drug no cerebrovascular or cardiac episodes attributable to this hypertensive overshoot have been reported. Caution has to be exercised in patients undergoing general anaesthesia, since such a hypertensive episode may complicate the anaesthetic. It is therefore recommended that clonidine be continued uninterrupted thoroughout the pre-, intra- and postoperative period, resorting to parenterally administered clonidine if oral administration is not feasible. The hypertensive overshoot itself usually responds readily to parenteral clonidine or β-adrenergic blocking drugs.

In conclusion, it was found that clonidine hydrochloride caused a significant antihypertensive effect on being added to the various antihypertensive regimens of these patients with problematical hypertension. Those with renal failure were satisfactorily managed by the addition of the drug, while its inclusion in regimens for malignant hypertension assisted improvement in the majority of cases. Its high rate of bothersome side-effects is compensated for by the relative safety on long-term administration.

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