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A PILOT STUDY OF ANTIHYPERTENSIVE THERAPY IN CEREBROVASCULAR DISEASE

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The value of antihypertensive therapy in patients with malignant hypertension has been well established (1, 2). In patients with less severe hypertension the mortality is reduced, mainly due to the decreased incidence of cerebral hemorrhage. This may be reflected in the decreasing mortality rate from stroke in the United States (3–6). However, the value of antihypertensive therapy for the treatment of moderate hypertension is not established, and its place in the treatment of cerebrovascular disease is hotly contended (7, 8). One retrospective review (9) of clinical records on patients treated for hypertension showed that in 80 patients who had experienced satisfactory reduction of blood pressure for a 68-month period there was no development of cerebral thrombosis, embolism or hemorrhage, whereas in 13 patients with similar initial high blood pressures followed for a comparable period, the blood pressure rose slightly and strokes developed.

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In another study (10) a comparison of 39 treated hypertensive patients with 42 untreated patients revealed that after three years of therapy with various antihypertensive drugs, the treated patients were similar in many respects to the untreated ones. Over the three-year period, however, the survival rate was 90 per cent in the treated group, with 2 fatal and 8 non-fatal strokes; in the untreated group the rate was 66 per cent, with 6 fatal and 22 non-fatal strokes. In a different study (11) of patients with diastolic hypertension in the range of 110 mm Hg or more, the subjects were assigned alternately to a group treated with antihypertensive drugs or to a control group that received no treatment for hypertension. Over a period of two to six years there were 4 strokes among the 30 treated subjects and 7 strokes among the 31 who were untreated.

Recently, a prospective study (12) was completed on 87 asymptomatic patients with moderate hypertension, some of whom were already receiving hypotensive drugs. On the basis of random drawing, half the patients were treated with antihypertensive agents and half were treated with matched placebos; some also received thiazides for congestive heart failure. In the treated group there was an adequate fall in blood pressure. In twenty-two months there were 2 strokes in the treated group and 1 stroke in the control group.

This brief review summarizes the presently available knowledge concerning the relationship between stroke and hypertension and suggests that control of moderate hypertension may prevent cerebrovascular hemorrhage, embolism and thrombosis. However, the value of controlling hypertension in subjects with moderate hypertension and cerebrovascular symptoms is by no means established and there is some evidence that lowering the blood pressure in such persons may make transient cerebrovascular symptoms worse.

These considerations led us to design a double-blind study of the use of antihypertensive therapy in patients *with known cerebrovascular disease* associated with moderate hypertension.

DESIGN OF STUDY

The patients were drawn from the Wayne County General Hospital, from the Hypertension Unit of the University of Michigan School of Medicine, and from the neurology clinics of the Detroit General Hospital and the Wayne Center for Cerebrovascular Research at Harper Hospital.

Selection of patients

The patients were admitted to the study if they had a permanent cerebrovascular deficit (cerebral thrombosis, hemorrhage or embolism) and/or a transient cerebrovascular deficit or transient ischemic attacks (TIA) within the preceding twelve months. The blood pressure had to be in the range of 150 to 200 mm Hg systolic and 90 to 120 mm diastolic. This was determined by review of the clinic records. Transient ischemic attacks were defined as episodes of definite focal neurologic deficit clearing entirely within twenty-four hours. There were no age limits. Subjects recently treated with hypotensive medication whose blood pressures were in the normal range were included in the study if there was a well documented history of pre-treatment hypertension meeting the requirements of the study.

The distribution of the 32 treated and control patients with respect to age, sex, race and duration of observation is shown in Table 1.

TABLE 1

	Antihypertensive Drug	Placebo
Number of patients	17	15
Months in study (mean)	9.7	11.1
Age (mean, yrs.)	57.7	46.5
Sex and Race:		
Negro males	3	2
Negro females	9	7
White males	4	4
White females	1	2

Pre-treatment evaluation

All subjects had a complete neurologic examination. With rare exceptions, the cerebrospinal fluid was examined for pressure, cellular content, protein content and serologic reactions for syphilis. Roentgenograms of the skull and electroencephalograms were also routinely obtained. The patients were admitted to the hospital at the beginning of the study and complete cerebral arteriograms were performed, with the exception of a few subjects who entered the study from the out-patient clinic. Cerebral radioisotope studies (radioactive mercury) were made in many cases. Determinations of blood urea nitrogen, uric acid, two-hour postprandial glucose and serologic reactions for syphilis were routinely made and repeated if necessary. When the subject was found suitable for the study, a two-week trial of the hypotensive medication was started and a one-page description was sent to the other participating investigators for their review. If it was unanimously agreed that the subject be accepted, he was assigned, in random manner, to either the treatment or the control group.

The controlled therapeutic program

After a satisfactory two-week therapeutic trial, a table of random numbers was used by the statistical consultant[1] to divide the patients into the two groups (treatment and control). This choice was not known to members of the study.

The treatment group received 1 tablet twice daily of the active drug which contained 0.5 mg of deserpidine and 5.0 mg of methyclothiazide.[2] The control group received one placebo tablet of identical appearance, twice daily. In the treated group, the aim was to control the systolic blood pressure (standing position) at a level of 140–160 mm Hg, with the use of 2 tablets daily. Medication was reduced to 1 tablet daily if the systolic pressure dropped below 110 mm; then the previous dosage was resumed once the blood pressure rose above that level. The subjects were examined at monthly intervals. The blood pressures were checked by three recordings with the patient in the standing position and three recordings with the patients in the supine position after a fifteen-minute rest. Initially, the blood pressures were checked in both arms; then the arm showing the higher reading was used for subsequent recordings. All pressures were recorded with the sphygmomanometer cuff at the level of the heart.

Neurologic evaluation for cerebrovascular symptoms

Every three months, or at any time when a patient reported a change in neurologic status, a complete neurologic examination was carried out. A neurologic scoring sheet was filled out; the graded scores ranged from 0 (death) to 100 (normal). This rating system placed strong emphasis on mental and performance status. Any subject was

[1] Dr. Richard Remington, School of Public Health, University of Michigan.

[2] Enduronyl-Forte, Abbott Laboratories, North Chicago, Ill.

withdrawn from the study if new cerebrovascular symptoms occurred with a neurologic deficit lasting more than twenty-four hours, or an incapacitating transient cerebral ischemic attack (TIA). Another cause for withdrawing a subject from the study was a rise in blood pressure above the study limits for two consecutive visits; the patient was then treated. This was an ethical decision in order to protect the patients from the known deleterious effects of severe hypertension. Only subjects with neurologic deficits were considered when the data were analyzed.

RESULTS

Table 1 shows the mean duration of observation for the treated and control groups. One patient was dropped from the study after eight months because of dangerously elevated blood pressure. The similarity of the initial blood pressure in the two groups and the values for the average blood pressure after three months of study are shown in Table 2. Resting blood pressures (patient supine) were used for all charts.

Table 3 shows the changes in mean blood pressure after seven months, and the clinical status at that time. The patients were divided into three groups:

Group I, with an average blood pressure of 180/107 mm Hg (mean, 143 mm).

Group II, with moderate hypertension; average blood pressure 163/105 mm Hg (mean, 134 mm).

Group III, with mild hypertension; average blood pressure 150/99 mm Hg (mean, 125 mm).

Patients in whom symptoms developed during the study

Group I, *L.D.*, a treated patient, had a cerebral thrombosis one and a half months after entering the study. Severe left hemiparesis, obtundation and aphasia developed. Her blood pressure at the time of the stroke was 170/104. The cerebrospinal fluid was normal. She was admitted to a nursing home. The neurologic deficit was still present when she was examined one week later.

Group I, *M.B.*, a treated patient, had a cerebral thrombosis five months after admission to the study. She was hospitalized by her physician but her records were made available to us. Her blood pressure was 170/90 on admission, at the time of right hemiparesis, which cleared after three days. The cerebrospinal

TABLE 2

Blood Pressure and Clinical Changes

	Antihypertensive Drug Group	Placebo Group
B.P., initial (avge.)	165/102 mm	161/106 mm
B.P., 3 months (avge.)	137/83	164/99
Cerebral thrombosis (No. of cases)	2	1
Worse; more TIA's	2	0
Unchanged	11	9
Unchanged but still having TIA's	2	2
Improved	2	5

TABLE 3

Blood Pressure and Clinical Status after Seven Months of Therapy

Patient	Initial Clinical Status	Sex/Age	Mean Blood Pressure (initial and 7-month change)	Placebo or Treatment	Clinical Status at 7 Months
Group I: avge. B.P. 180/107; mean B.P. 144					
ES (W)	TIA*	M/59	145 +5	P**	Unchanged; occasional TIA's
RE (N)	Thr.	M/51	140 −41	P	Unchanged
EH (N)	Thr.	M/64	140 +20	P	Unchanged
			(avge. −5)		
EM (W)	Thr.	M/38	148 −13	T	Unchanged
SZ (W)	Thr.	M/72	148 −22	T	Unchanged
LD (N)	Thr.	F/60	148 −11	T	CVA at 1.5 months; dropped from study
EW (N)	Comb.	F/61	146 −41	T	Unchanged; TIA's in same freq.
HL (W)	Thr.	M/62	145 −15	T	Unchanged
MB (N)	Thr.	F/64	140 +6	T	CVA at 5 months; dropped from study
HG (W)	Thr.	M/63	140 −37	T	Unchanged; slightly depressed
			(avge. −19)		
Group II: avge. B.P. 163/105; mean B.P. 134					
CW (N)	Thr.	F/78	138 +12	P	Improved (mentation)
LL (W)	Thr.	M/46	135 −14	P	Unchanged
GC (W)	Thr.	F/48	135 −22	P	Unchanged
HD (W)	TIA	M/64	134 +12	P	Unchanged; no TIA's
MH (N)	Thr.	F/41	133 −8	P	Unchanged
MMi (N)	Thr.	F/46	130 +2	P	CVA at 7 months; dropped from study
GCy (W)	Thr.	F/72	130 +35	P	Improved (ambulation) but dropped from study at 8 months because B.P. rose too high
			(avge. +1)		
CL (N)	TIA	M/59	138 −45	T	Worse due to incr. TIA's; dropped from study at 8 months
JM (W)	Comb.	F/52	136 −30	T	Worse due to incr. TIA's; dropped from study at 2 months
LK (N)	TIA	M/66	133 −15	T	Unchanged; no TIA's
			(avge. −30)		
Group III: avge. B.P. 150/99; mean B.P. 125					
MF (N)	Thr.	F/42	130 −9	P	Improved (mentation and ambulation)
MMy (N)	TIA	F/51	128 −2	P	Unchanged; TIA's in same freq.

TABLE 3—*Continued.*

Patient	Initial Clinical Status	Sex/age	Mean Blood Pressure (initial and 7-month change)	Placebo or Treatment	Clinical Status at 7 Months
Group III: avge. B.P. 150/99; mean B.P. 125 (Continued)					
LB (N)	Thr.	F/50	127 −1	P	Unchanged
SS (N)	Thr.	F/43	115 +17	P	Unchanged
VM (N)	TIA	F/42	128 −22	T	Improved; no TIA's
PT (N)	Thr.	F/63	125 −6	T	Unchanged
CD (N)	Thr.	F/53	125 −12	T	Unchanged
AE (N)	Thr.	F/67	120 +15	T	Improved (mentation)
BH (N)	TIA	F/32	116 +13	T	Unchanged; rare TIA's
NB (N)	Thr.	M/61	115 −10	T	Unchanged; slightly depressed
			(avge. −4)		

* TIA = Transient ischemic attacks.
Thr. = Cerebral thrombosis.
Comb. = Complete stroke plus TIA's.

** P = Placebo.
T = Treatment with antihypertensive drug.

fluid was not examined. When she was seen a few weeks later in the clinic, she had recovered to the level of her neurologic status before entering the study. Although she had been taking the active drug, her blood pressure had risen by the time of her clinic visit prior to the stroke.

Group I, *E.W.* In this patient, transient ischemic attacks developed during hypotensive therapy. She had attacks of vertigo and ataxia when her blood pressure was reduced below 126/88 mm.

Group II, *M.Mi.* was treated with placebo and experienced an episode similar to that of M.B.—with full recovery from left hemiparesis after four days.

Group II, *J.M.* and *C.L.* were patients with vertebro-basilar insufficiency manifested by intermittent vertigo and ataxia during active hypertensive therapy. Both became symptomatically worse when the blood pressure was reduced; the frequency of transient cerebral ischemic attacks, was greatly increased and the patients had to remain in bed. They recovered to the level of their previous status when the drug was discontinued.

Group II, *G.Cy.* was dropped from the study after eight months of placebo therapy because her blood pressure rose to a dangerously high level and was still elevated at the time of a second visit two weeks later. She was asymptomatic during this period except for a residual hemiparesis present before admission to the study.

Group I *H.G.* and Group III *N.B.* manifested mild depression due to deserpidine. H.G. responded to low doses of methylphenidate hydrochloride. N.B. required no treatment, as the depression cleared spontaneously.

The numbers of subjects remaining unchanged were similar in the treated and placebo groups (Table 2). In each group there were 2 patients whose transient cerebral ischemic attacks (present before treatment) continued unchanged. Two patients improved in the treated group, and 5 in the placebo group. Improvement was mainly due to improved mentation and ambulation.

General observations

A pronounced fall in blood pressure did not necessarily cause a dangerous increase in the recurrence rate of cerebrovascular episodes, and active treatment did not invariably reduce the blood pressure. Several patients showed a rise in blood pressure despite antihypertensive therapy. The neurologic score sheet appeared to be a reliable method for following the patients. A change in overall score amounting to 3 points was found to be significant and reproducible by all observers independently. An 8-point decrease in the score was usually regarded as sufficient to warrant discontinuing the subject from the study (13). Most of the severe neurologic deficits in either medication group occurred in the subjects with higher blood pressure levels.

DISCUSSION

Three aspects of antihypertensive therapy were considered to be of prime importance for analysis: 1) the effect on patients with previous strokes and neurologic deficits, 2) the effect on patients with transient ischemic attacks, and 3) the effect on the mental function of elderly patients with cerebrovascular disease. To date, the data are insufficient to provide firm conclusions, but the method of study appears feasible.

Experimental work has shown that neurologic symptoms can be reproduced by vasospasm in animals made acutely hypertensive, and that this effect is reversible when the blood pressure is lowered (14, 15). Ross Russell (16) reemphasized the occurrence of atherosclerosis of the Circle of Willis in hypertensive patients and confirmed that miliary microaneurysms are often found; the microaneurysms might not be able to withstand even moderate hypertension. Recent retrospective studies of patients with cerebral infarction indicated that they fall into two groups: 1) those with diastolic pressures below 110 mm, who have a tendency toward large-vessel stenosis in the neck and the development of massive infarction and cystic areas; and 2) those with diastolic pressures above 110 mm, who have mainly small ischemic softenings, small misdiagnosed intracerebral hemorrhages and a small proportion of extracranial stenotic lesions (17, 18).

Attempts to induce transient ischemic attacks regularly in patients with TIA histories, by provoking hypotension with the use of hexamethonium and a tilt-table, have resulted in failure (19). This procedure produced mental changes, light-headedness and confusion, but no focal ischemic attacks. Similar results were reported when hypotension was induced deliberately during surgery (20). Treatment of elderly hypertensive subjects with a reserpine-hydrochlorothiazide combination failed to induce significant changes when compared to results in a control group (21).

Several recently reported studies give some indication of the size of the sample and the length of follow-up needed for a conclusive study of this type. A study of 158 subjects with cerebrovascular symptoms showed that when strokes developed after transient ischemic attacks, the patients had had the warning symptoms for an average of eighteen months before the major episode (22). A retrospective study (23) demonstrated that in a large group of hypertensive patients treated with various antihypertensive agents the occurrence rate of neurologic deficits lasting up to one day was 15 per cent, and of deficits lasting more than one day, 26.5 per cent; the study lasted twenty-three and a half months.

The Veterans Administration Cooperative Study on Atherosclerosis involved a double-blind study of the effects of estrogens in men with cerebral infarction caused by atherosclerosis (24). There were 582 patients, followed for an average of 16.7 months—287 in the control group and 295 in the treated group. During this period there was a 10.3 per cent recurrence of cerebral infarction and an 11.5 per cent recurrence of transient cerebral ischemia; the rates were not significantly different in the two groups.

A minimum 10 per cent recurrence rate of stroke per year can be predicted. If it were postulated that specific treatment would cause a 50 per cent reduction in the stroke recurrence rate, then 600 patients would be needed (300 each for treatment and control groups) to show a statistical difference (24). The figure of 50 per cent reduction is an arbitrary one chosen for the sake of statistical projection and does not imply any actual expectation. The present study was a planned feasibility trial prior to a planned cooperative study designed to answer the question: "Does the administration of antihypertensive drugs to patients with moderate hypertension and cerebrovascular disease affect the recurrence rate of cerebrovascular symptoms?" Such a planned national cooperative study seems feasible and is now underway (Cooperative Study—Cerebrosvascular Disease and Hypertension—PRS-IROINB-HE-16944-01).

SUMMARY

A controlled double-blind study was conducted on 32 patients with mild to moderate hypertension and recent cerebrovascular symptoms. The effects of antihypertensive therapy (deserpidine-methyclothiazide combination) on the recurrence rate of cerebrovascular symptoms were assessed. During 10.8 months of observation there was no difference in the recurrence rate between the two groups. The blood pressure response was evaluated at seven months; for the control group the average reading was 164/99 mm and for the treated group, 137/83 mm. Two patients receiving antihypertensive therapy showed a side effect—minimal depression. The methods developed in the study are described.

No specific conclusions can be drawn from such a small sample and the limited period of observation. Extension of this type of study seems indicated and has been shown to be feasible. Our findings are presented as a pilot study of a projected cooperative program in which it is planned to use the methods developed, to provide sufficient information for defining the value of antihypertensive therapy in patients with cerebrovascular symptoms.

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