Clinical observations on a new antihypertensive drug, 2-(2, 6-dichlorphenylamine)-2-imidazoline hydrochloride*

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Establishing an effective therapeutic regimen in cases of severe hypertension continues to be a highly individualistic process of balancing side effects against blood pressure response. Sympathetic blocking agents, needed in most cases of severe hypertension, often disable the patient by causing an orthostatic hypotension as the price he must pay for a partial reduction of recumbent blood pressure.

During the past several years, a new antihypertensive agent, 2-(2,6-dichlorphenylamine)-2-imidazoline hydrochloride (Catapres), has been under clinical study.[1] The mode of action of this drug has not yet been defined,[2] but it has been shown to be effective and relatively safe, with drowsiness as its major side effect. Most important, the new agent is reported to lower recumbent and standing blood pressures equally well throughout the day, without the wide diurnal variations that induce excessive orthostatic hypotension when the patient rises in the morning, but it fails to prevent nocturnal recumbent hypertension. Although metabolic side effects from Catapres have not been noted in clinical reports, a slight diabetogenic tendency has been observed in some species of animals.[3]

The study reported here was designed toward three specific objectives: (1) to test the agent alone in subjects with mild hypertension in order to examine its reported ability to lower recumbent blood pressure without creating postural hypotension; (2) to test long-term efficacy and acceptability of the agent for severely hypertensive patients intolerant of conventional sympathetic blocking agents; (3) to evaluate the frequency and acceptability of various side effects and to examine the drug's effects on liver and hematopoietic function and on carbohydrate metabolism.

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Methods

Sixteen patients, ranging in age from 27 to 65 years, were studied. They were divided into two groups on the basis of relative severity of hypertension. Group 1 included 6 patients with mild blood pressure elevation, who had recorded their blood pressure at home for several weeks preceding the drug trial. These patients were given Catapres alone for a period of one month, the studies being directed chiefly at the effects of the drug on carbohydrate metabolism. Group 2 comprised the remaining 10 patients, who had had severe postural hypotension or were otherwise refractory to treatment with the usual sympathetic blocking agents. Background diuretic therapy was maintained in all these patients, who were treated with Catapres alone for periods of 5 to 11 months. All the patients were admitted to the Clinical Research Unit of the University of Michigan Hospital for the initiation of Catapres treatment and were discharged in 5 to 6 days.

Carbohydrate tolerance was tested in subjects belonging to Group 1 as follows. Prior to hospital admission they were placed on a 300 Gm. carbohydrate diet for three days. After admission, the tolbutamide tolerance test and the intravenous glucose tolerance test were performed. Then an oral test dose of Catapres, 0.150 mg., was given and the effects on blood pressure were noted. Based on the response observed, an appropriate treatment regimen was established and the tolbutamide test was then repeated on the fourth or fifth day of therapy in the hospital. The individual's glucose tolerance was re-examined on the second day of inpatient treatment and at the end of a month of outpatient treatment with Catapres, three days after the preparatory diet had been reinstituted. The intravenous test dose was administered in the morning in the fasting state, two hours after drug ingestion.

The more severely hypertensive subjects belonging to Group 2 were handled as follows. After other antihypertensive drugs, except diuretics, had been discontinued, an oral test dose of Catapres was administered and subsequent dosage in

Table I. Effect of dichlorophenylamine imidazoline (Catapres) on blood pressure initially and after one month

Case No.	*Patient's age*	*Inpatient BP (mm. Hg)*				*Change in morning home blood pressures* (mm. Hg) (Average of last 5 days compared to pretreatment status)*		
		Last BP before test dose		*Maximum decline with first test dose 0.150 mg.*		*1 month after drug*		*Daily dose (mg.)*
		R	*S*	*R*	*S*	*R*	*S*	
1	65	180/110	165/100	−20/−15	−20/0	+8/−22	+13/−8	0.375
2	50	150/100	135/110	−35/−20	−25/−15	*Discontinued Rx†*		
3	48	170/100	140/105	−45/−20	−20/−35	+5/−12	+3/−7	0.150
4	27	185/125	165/125	−40/−30	−55/−30	−41/−16	−38/−25	0.375
5	38	195/145	165/130	−55/−55	−35/−25	−21/−15	−6/−7	0.300
6	49	195/125	205/103	−45/−30	−55/+7	+13/+3	+5/−3	0.300
Average changes				−40/−28	−35/−16	7/12	5/10	

*Average of last 5 readings at home in pretreatment phase compared to last 5 morning readings at home before returning to clinic at one month. Blood pressure taken in recumbency (R) or standing (S).

†Complained of drowsiness and depression. Drug discontinued before return visit.

Table II. Effect of Catapres on carbohydrate metabolism

Case No.	Fasting blood sugar						Daily dose (mg.)	Intravenous glucose tolerance test: Change in K value after Catapres†	
	Related to test dose				On therapy				
	Before		After		+3-4 days	+30 days			
	−2 day	−1 day	2 hrs.	+1 day				1 day*	30 days
1	96	96	90	74	90	80	0.375	−0.03	−0.19
2	83	80	98	95	80	—	0.300	+0.19	—
3	92	80	82	74	78	70	0.150	−0.02	−0.11
4	82	78	76	84	82	81	0.375	+0.09	+0.31
5	80	82	78	85	75	—	0.300	+0.26	—
6	88	75	80	80	80	90	0.300	−0.16	−0.03
Mean	86.8	81.8	84.0	82.0	80.8	80.3	0.300	+0.06	0.00
Sign $p < 0.05$	NS	NS	NS	NS	NS	NS			

*Fasting blood sugar drawn 2 hours after oral administration of drug. Test dose of drug was 0.150 mg.
†K value expresses the slope of disappearance of the glucose solution (25 mg. per kilogram) injected at time "0". Samples taken at 10, 20, 30, 40, 50, and 60 minutes. A negative change in K value denotes a slower rate of removal of administered glucose. Changes observed are within the limits of normal variation.

Table III. Replacement of conventional drugs with Catapres in severely hypertensive patients

Case No.	Status of blood pressure								Principal side effects	
	Pretreatment: Hospital admission BP recumbent	On usual drug therapy*			On Catapres					
		Outpatient BP		Daily dose (mg.)	Outpatient BP		Duration on Catapres (mo.)	Daily dose (mg.)		
		Recumbent	Standing		Recumbent	Standing			Usual drug	Catapres
Guanethidine										
7	250/140	190/135	100/ 70	100	178/130	192/140	7	0.900	A.M. syncope	Constipation
8	250/160	232/123	116/ 68	75	192/128	192/132	7	0.900	A.M. syncope	Constipation
9	260/170	190/100	160/100	50	146/ 94	120/ 90	10	0.900	Diarrhea	0
10	250/140	230/130	160/100	100	232/128	198/128	5†	1.200	A.M. syncope	0
11	280/165	217/113	208/130	100	152/ 86	150/120	10	0.400	None	0
Alpha-methyldopa										
12	240/138	200/130	170/104	1,500	154/ 88	142/ 94	11	0.500	A.M. syncope	Drowsiness
13	218/110	240/110	180/124	1,500	184/102	167/108	10	0.500	Dizziness	Drowsiness
14	208/150	186/109	174/120	1,500	180/100	192/108	11	1.200	None	None
15	240/130	198/113	160/114	2,000	164/104	146/104	7	0.525	Fatigue	None
Reserpine										
16	260/140	180/100	168/106	0.25	168/108	138/ 98	9	0.700	Depression	None

*All patients received maximally effective dosage of a thiazide or chlorthalidone throughout the study.
†Blood pressure uncontrollable with Catapres alone. Trial discontinued after 5 months.

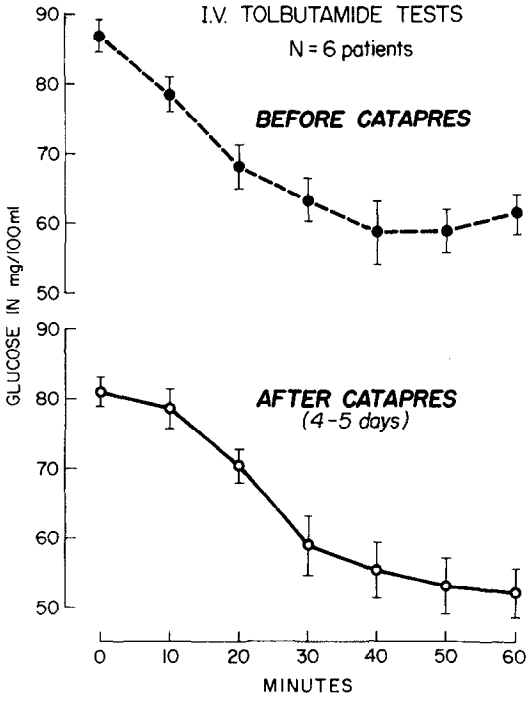

Fig. 1. Response to tolbutamide before and after Catapres. Vertical bars indicate standard error of the mean for each observation. See text for details.

the hospital was adjusted to bring about a maximal blood pressure reduction within the patient's tolerance to side effects. The patients were then followed in the outpatient clinic at monthly intervals. They continued to take their diuretic drugs without change, but their dosage of Catapres was readjusted in accordance with the blood pressure as recorded at home and in the clinic.

Results

The first oral test dose of 0.150 mg. of Catapres regularly lowered the blood pressure of patients in Group 1, the average decline being −40/−28 mm. Hg recumbent and −35/−16 mm. Hg standing (Table I). The maximum decline occurred between the second and third hour, with offset of action at four to six hours. At the end of one month, the drug in the original dose appeared to lose some of its antihypertensive effectiveness.

These patients were studied primarily to evaluate the short-term effect of the drug on glucose tolerance. The metabolic tests were applied at the time interval when a slight hyperglycemic influence had been noted in the dog studies.[3] Table II shows that the drug had no effect on the fasting blood sugar or on the intravenous glucose tolerance test. The influence of the drug on insulin release was studied using the tolbutamide test. There was no indication of any consistent diabetogenic trend which might be attributed to the drug (Fig. 1).

Long-term effects. After 5 to 11 months of therapy with Catapres and a diuretic, most patients achieved a blood pressure level comparable to or better than that recorded with prior conventional antihypertensive treatment. Dosage of the new drug was gradually increased as side effects wore off. A dose of 0.5 to 1.2 mg. daily served to replace such other agents as alpha-methyldopa (1.5 to 2.0 Gm. daily) or guanethidine (50 to 100 mg. daily), with respect to maintaining similar blood pressure levels (Table III). Disabling postural hypotension, occurring with the previous regimens in Patients 7 and 8, were much less apparent on Catapres at approximately the same levels of recumbent blood pressure. Blood pressure control was somewhat erratic; home blood pressures were generally lower than the clinic readings, taken two hours after ingestion of the morning dose of drug. Patients 9, 11, 12, and 16 derived clear benefit from the conversion to Catapres. The other patients had generally lower home blood pressures, but they were not necessarily better controlled on the new regimen. These cases were chosen because their blood pressure was refractory to prior sympathetic blocking agents, or they were disabled by orthostatic hypotension. It is therefore not surprising that the new drug did not benefit all the patients.

Side effects. The most common reaction was drowsiness which was usually transient and did not cancel the patient's ability to mobilize his attention to sudden crises. Drowsiness became less evident with continued use of the drug, but initially it was the chief limiting factor to the size of dose which the patient would accept. At night, however, this side effect became advan-

tageous, since a larger dose at bedtime resulted in good sedative effects and appeared to exert some influence on the morning blood pressure reading. Dry mouth was a minor complaint in most cases; constipation was easily controlled by laxatives.

Marked bradycardia was noted only occasionally in our series and seemed quite variable. One patient, No. 13, taking 0.6 mg. a day, telephoned to report that his pulse had fallen to 42 beats per minute but was regular. An electrocardiogram taken one-half hour later showed a sinus rhythm with a rate of 66.

In the majority of patients, after 6 months or more of treatment, the side effects were greatly diminished and rarely disabling, although the effects on blood pressure remained, as evidenced by a prompt rise in blood pressure during a brief substitution of a placebo for the active drug. None of the patients on long-term treatment, most of whom had been converted from conventional medication because of side effects, elected to discontinue Catapres when given this option. No evidence of progression of the cardiac or renal complications of their disease was noted. The fasting blood sugar at the end of the observation period was unchanged from the pretreatment values.

Renal, hepatic, and hematopoietic function was unchanged for periods of treatment up to 11 months, as judged by serial determination of blood urea nitrogen (BUN), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, hematocrit, hemoglobin, and leukocyte and differential cell counts.

Discussion

To achieve general usage among current antihypertensive agents, a drug must be shown to be safe and continuously effective in reducing blood pressure. Catapres fulfills the criteria of long-term effectiveness and no long-term toxicity developed in 10 patients observed for a median period of 9 months. While the short-term low-dosage study detailed in Table I suggests that alone the drug loses some of its initial effectiveness, our later experience giving Catapres in combination with diuretics indicates that as side effects become less prominent dosage may have to be increased, but that eventually one reaches a stable dosage level which maintains antihypertensive effectiveness. A potential advantage of this agent over sympathetic blockers is that it does not interfere with postural reflexes. The chief disadvantage is that it is not as potent or as continuously effective as guanethidine, for example.

For these reasons we believe Catapres will be useful in the management of selected cases of moderately severe hypertension, particularly where sympathetic blockers are needed, but cause severe postural hypotension.

Summary

The drug 2-(2,6-dichlorphenylamine)-2-imidazoline hydrochloride, available as Catapres, was given to 16 patients with established hypertension. Six patients were studied for one month to detect abnormalities in carbohydrate metabolism. None were found. Ten severely hypertensive patients were maintained for from 5 to 11 months on Catapres and diuretics.

In a single dose, Catapres invariably lowered the blood pressure significantly, but without producing orthostatic hypotension. The maximum effect occurred between 2 and 3 hours after ingestion of the drug. The duration of drug action was 4 to 6 hours.

In long-term treatment of ten patients, Catapres, combined with a diuretic, proved to be as effective as a diuretic plus guanethidine or Aldomet, which the patients had previously been taking. A dose of 0.400 to 1.200 mg. of Catapres was equivalent to 1.5 to 2.0 Gm. of Aldomet or 50 to 100 mg. of guanethidine.

The chief side effect of the drug was drowsiness, but this was not incapacitating, it did not require cessation of treatment, and it became less prominent with the passage of time. In patients who had experienced severe orthostatic hypotension on other drug regimens, the condition was considerably relieved by Catapres. No signs of toxicity were noted, as judged by carbohydrate tolerance, BUN, SGPT, alkaline phosphatase, and hematologic determinations.

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