1-Hydrazinophthalazine (Apresoline in the) Treatment of Hypertension: A Two Year Study

By Joseph H. Hafkenschiel, M.D., and M. August Lindauer, M.D.

Patients with severe essential hypertension have been carefully studied periodically in an attempt to group them as to probable life expectancy. Forty such patients have been observed while on oral 1-hydrazinophthalazine and a low salt diet. Nineteen of the 33 patients in the groups having a relatively good prognosis for survival had some decrease in diastolic pressure. Only one of seven patients in Smithwick group IV had a satisfactory reduction in blood pressure.

This report concerns our experience during a period of two years with 1-hydrazinophthalazine (Apresoline) and a low salt diet in 40 patients. All have been on this program for at least one year. They have been grouped as to life expectancy, according to Smithwick's classification.

A comparison of survival rates after thoracolumbar sympathectomy, and after medical therapy in similar hypertensive patients, suggests that surgical treatment may improve the group life expectancy of patients with certain severe vascular complications (Smithwick group IV). Following sympathectomy, however, the number of patients who are dead five years after operation is high. We were particularly interested in those patients who might be expected to do poorly with sympathectomy. Could these be benefited by any one, or a combination, of the newer depressor drugs?

The depressor properties of Apresoline were discovered in the course of testing of antimalarial drugs. The reduction of both systolic and diastolic pressure in animals, by an action largely central, without a sedative component, led to measurements of renal blood flow during the hypotension induced by parenteral doses of the drug in both normotensive and hypertensive patients. The increase in renal blood flow observed in hypertensive patients was followed by studies of the influence of this drug on vasoconstrictor reflexes in man. Apresoline appears to suppress the outflow of sympathetic vasopressor impulses.

We observed a reduction of blood pressure both supine and standing after intramuscular injection and an increased renal blood flow in an acute experiment in one patient with azotemia (table 1). A decreased cerebral vascular resistance was obtained in seven patients with moderate hypertension (table 2). These acute experiments led to a prolonged study of the oral effectiveness of 1-hydrazinophthalazine in patients with essential hypertension.

Methods

Forty outpatients were evaluated in the fashion previously reported. All were placed on Apresoline plus a salt restricted diet for at least one year. Sufficient observations and repetition of tests were made to permit grouping as to life expectancy according to the criteria of Smithwick. The number of patients of both sexes in each of the four groups is shown in table 3.

Those who have continued to take the drug for at least one year have been evaluated by monthly visits to the Hypertension Clinic. The morning dose of the drug was ingested about one hour before reporting to clinic. At each clinic visit the blood pressure was checked after a 10-minute rest, using a postural test. At six-month intervals the following examinations were repeated: retinoscopy, electrocardiogram, orthodiagram, intravenous phenol-
Table 1.—Effect of an Intramuscular Injection of 20 mg. of Apresoline on Renal Hemodynamics and Mean Arterial Pressure in a Young Male (Smithwick Group IV) with Mild Azotemia

<table>
<thead>
<tr>
<th></th>
<th>Before Apresoline</th>
<th>90 Minutes After Apresoline</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Urea Clearance</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Plasma Creatinine</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>PSP</td>
<td>10% in 15 minutes</td>
<td></td>
</tr>
<tr>
<td>CPAH</td>
<td>195</td>
<td>250</td>
</tr>
<tr>
<td>Renal Blood Flow</td>
<td>295</td>
<td>380</td>
</tr>
<tr>
<td>Mean Blood Pressure</td>
<td>130</td>
<td>115</td>
</tr>
<tr>
<td>Filtration Fraction</td>
<td>.28</td>
<td>.21</td>
</tr>
<tr>
<td>Renal Peripheral Resistance</td>
<td>.45</td>
<td>.30</td>
</tr>
</tbody>
</table>

* These studies indicate a rise in renal blood flow and a fall in renal peripheral resistance.

This study was performed by Drs. John K. Clark and A. P. Crosley and was supported in part by the National Heart Institute, U. S. Public Health Service.

Table 2.—Effect of Intramuscular Injection of 10 to 20 mg. of Apresoline on Cerebral Hemodynamics and Oxygen Metabolism in Patients with Minimal Vascular Complications 60 Minutes after the Initial Study†

<table>
<thead>
<tr>
<th>Pressure</th>
<th>Flow</th>
<th>Resistance</th>
<th>Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>8 Obsns. 7 patients</td>
<td>144</td>
<td>113</td>
<td>56</td>
</tr>
<tr>
<td>Change after Apresoline</td>
<td>31 ± 20</td>
<td>1 ± 0.7</td>
<td>0.5 ± 0.4</td>
</tr>
<tr>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Pressure was measured by a damped mercury manometer through the indwelling femoral artery needle. The figures in the first horizontal line on the left are the group averages during the initial study and 60 minutes after Apresoline. Cerebral blood flow and oxygen uptake were measured by the nitrous oxide technique of Kety and Schmidt. Resistance is the pressure divided by flow. The figures in the second horizontal line of each column represent the mean change and the standard deviation of the individual differences. The only statistically significant reductions were in the mean arterial pressure and cerebral vascular resistance.

sulfonphthalein (PSP) test, urinalysis, hemoglobin and leukocyte count, and blood urea nitrogen (if elevated initially).

**Dosage Schedule.** Most patients were started on a dose of 25 mg. four times daily. The dose was increased gradually until either a satisfactory fall in blood pressure was obtained, or a maximum dose of 200 mg. four times daily was reached. The effective dose ranged from 75 mg. to 200 mg. repeated either

<table>
<thead>
<tr>
<th>Smithwick Group</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>19</td>
</tr>
</tbody>
</table>

![Fig. 43 w f](http://circ.ahajournals.org/)

Fig. 1. Blood pressure observations, supine and standing, for three minutes in a female patient of group II having a satisfactory reduction while on oral Apresoline for 24 months. Treatment was initiated while the patient was hospitalized as denoted by the arrow. The peaks in pressure late in this period were observed when Apresoline was withheld so that laboratory tests could be performed.

three or four times daily. The average dose was 125 mg. four times daily, as noted by Grimson.13

**Placebo Medication.** Inactive tablets were substituted for Apresoline in six cases for periods of from one to two months. In each instance, there was a rise in both systolic and diastolic pressures. Reduction to the former level was observed when the previous dosage of Apresoline was again reached (figure 1). It is our observation that, upon returning to Apresoline, small dosages should be used and gradually increased. There is apparently an unusual susceptibility to side reactions at this time.
Results

Depressor Properties. The effects upon blood pressure in relation to the Smithwick classification are presented in table 4. There were 9 patients in group I, 17 in group II, 7 in group III, and 7 in group IV.

Improvement in blood pressure was arbitrarily considered to have occurred if there was a fall in supine diastolic pressures from 120 mm. Hg or higher to 110 mm. or lower on at least two outpatient visits. The majority of these patients before treatment had diastolic pressures above 130 mm. Hg.

Fifteen out of 26 in group I and II showed this degree of fall in blood pressure. The favorable response of a group II patient is shown in figure 1. In group III there were favorable reductions in four of seven patients, and in group IV, in only one of seven. The blood pressure response of this latter patient is shown in figure 2. The fall in blood pressure after three minutes of quiet standing was not strikingly different from the resting blood pressure in any of our patients.

Evidence of Clinical Improvement. The course of vascular complications is summarized in table 4. No improvement in renal function, as measured by the 15-minute excretion of intravenously administered phenolsulphonephthalein was observed. Most of these patients had an initial 15-minute excretion of better than 20 per cent. There was no evidence of progressive renal damage during administration of the drug. No patients were observed to have a reduction in heart size as indicated by decrease in frontal surface area of 30 per cent or more plus a decrease in transverse cardiac diameter of more than 3 cm. from the predrug orthodiagram measurement. Only four patients were observed to have improvement in retinopathy* according to Keith and Wagener's classification. Three of these patients were in the Smithwick groups I and II classification, and one was in group III. The changes in this small group of patients are to be contrasted with the unchanged eye grounds of 30 patients. It is of interest that six patients showed advancing retinopathy during this period of observation.

In the electrocardiogram of three patients, inverted T waves became upright or S-T segment displacement reverted to the iso-electric line.

Three women, all over age 45, in this group of 40, had initial slight nitrogen retention (20 to 30 mg. per 100 cc.) and all are still living with essentially the same degree of azotemia after one year of Apresoline therapy.

Tolerance. In our experience the hypotensive response to oral Apresoline appeared to persist

*These examinations were made by Dr. George S. Tyner, Department of Ophthalmology, Hospital of the University of Pennsylvania.
for as long as the drug was continued. A rise in pressure during treatment was usually corrected by an increase in dosage. Contrarily, several patients have required a reduction in maintenance dosage. (See fig. 2.)

Side Reactions. Usually side effects appeared just after the initiation of therapy and subsided within a week or two. Tachycardia was invariably produced. In some cases where headache was particularly bothersome, Pyribenzamine or Benadryl was prescribed with the Apresoline and afforded relief.16 The symptoms reported by the 40 patients were (table 5): headache, 15 cases; tachycardia and palpitation, seven cases; nausea and vomiting, five cases; and urticaria, cutaneous flushing and lacrimation, one case each. Sixteen patients have been unable to tolerate Apresoline for as long as one week. Severe headache and palpitation accompanying the tachycardia were the most frequent reasons for discontinuing its use. Recently we have encountered less difficulty when using a lower initial dosage of 12.5 mg. four times daily for the first 10 to 14 days.

Toxicity. Prolonged administration of Apresoline has not produced toxic reactions attributable to a cumulative effect. No attempt was made to determine any specific effect of the drug on blood cell morphology or liver function.

Mortality during Therapy. The only death observed in this group was that of a 59 year old white man with symptoms of mild angina who had been on Apresoline for 12 months. This patient had grade III retinopathy, slight cardiac enlargement, and electrocardiogram showing slight changes characteristic of the hypertensive state, blood urea nitrogen of 14 mg. per 100 cc. with 30 per cent phenolsulphonphthalein excreted in 15 minutes. Thus, the patient was in Smithwick group III. The initial blood pressure while hospitalized was 200/130 and on a dosage of 50 mg. three times each day this pressure decreased to the range of 180/105 as an outpatient. Each attempt to increase the dosage beyond this led to headache. The patient was placed on a placebo and an increase of pressure was observed. Shortly after resuming Apresoline therapy, he developed a clinical picture suggesting coronary thrombosis and died. Post-mortem examination was not made. It is our impression that this was a coincidence rather than a result of therapy by contrast with some of the deaths discussed in Grimel's report.11

| Table 5.—Numbers Who Reported Unpleasant Reactions in This Study of 40 Patients |
|---------------------------------|-----|-----|
| Headache                        | 15  | 38% |
| Palpitation                     | 7   | 18% |
| Nausea and Vomiting             | 5   | 12% |
| Urticaria                       | 1   | 2%  |
| Flushing                        | 1   | 2%  |
| Lacrimation                     | 1   | 2%  |

Comment

We have not observed progressive vascular damage among the 33 patients in groups I, II and III (Smithwick) while on the program of oral Apresoline. Fifty-seven per cent of the patients in these groups have had a satisfactory reduction in blood pressure. In five of these patients there has been an improvement in the vascular complications noted before drug treatment was initiated. The fact that about 25 per cent of all patients started on this drug have remained on it for at least a year suggests that these patients were not seriously disturbed by the unpleasant aspects of this therapeutic program.

Our present impression is that the patient with minimal evidence of progression in vascular complications may be given oral Apresoline and a low salt intake so long as there is no evidence indicating further progression of damage. If clinical and laboratory data indicate increasing damage, and particularly if renal function measurements suggest further deterioration, we believe these signs warrant more drastic steps in treatment, with a trial of other potent experimental drugs.5, 13, 17 Surgical intervention18-20 is to be considered if these are likewise unsuccessful.

What we most need to know is: (a) Does Apresoline or any other depressor drug keep mild hypertensives from getting worse and thus obviate surgical intervention? (b) Does Apresoline prolong the lives of those with severe hypertension whose azotemia precludes
operation? It is obvious that a longer period of observation in a larger series of patients is needed before these questions can be answered.²¹

SUMMARY

1. Oral Apresoline was an effective depressor agent in 57 per cent of hypertensive patients having a relatively good prognosis for survival, who took the drug for at least one year.

2. Among seven patients having the poorest survival prediction, only one individual had a reduction in blood pressure considered to be favorable.

3. The period of observation of the present study was too short to indicate whether or not Apresoline has favorably affected the natural history of hypertensive vascular disease.

4. We suggest that patients with severe essential hypertension, having good renal, cardiac and retinal findings, are suitable candidates for a trial of oral Apresoline. This agent may be continued so long as there is no evidence of progression as determined by periodic re-evaluation.

ACKNOWLEDGEMENTS

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SUMARIO ESPAÑOL

Pacientes con hipertensión esencial severa han sido cuidadosamente estudiados periódicamente en un esfuerzo para agruparlos de acuerdo a la expectativa de duración de vida. Cuarenta casos han sido observados en un regimen de Apresoline oral y dieta baja en sal. Diez y nueve de los 33 en el grupo con un pronóstico de vida relativamente bueno han tenido alguna diminución en la presión diastólica. Solamente uno de siete pacientes en el grupo correspondiente a Smithwick grupo IV ha tenido una reducción satisfactoria en presión arterial.

REFERENCES

¹ SMITHWICK, R. H.: The effect of sympathectomy upon the mortality and survival rates of patients with hypertensive cardiovascular disease.


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