The Effect of 1-Hydrazinophthalazine in Hypertension

By Henry A. Schroeder, M.D.

The compound 1-hydrazinophthalazine appears to be an antihypertensive drug of only moderate potency. Based on experience with 50 cases of arterial hypertension, it was found most effective in patients with unsuccessful sympathectomy, malignant hypertension, and neurogenic hypertension. It was relatively ineffective in renal hypertension and in a group of miscellaneous conditions. Chronic administration by mouth in outpatients was feasible.

A new compound, 1-hydrazinophthalazine (C-5968), has been shown by Reubi1 to cause hemodynamic effects which suggest that it may act as an antihypertensive agent. After single doses effective renal plasma flow was increased, while blood pressure was moderately lowered in hypertensive patients.1 Freis and Finnerty2 found that the cold pressor test was modified by the drug, as well as the vasopressor “overshoot” following the Valsalva maneuver. Pulse volume in digits also increased. Grimson and his co-workers3 failed to demonstrate sustained effects on repeated administration.

1-Hydrazinophthalazine is the basic structure (fig. 1) for several substituted compounds which have the peculiar pharmacologic properties of increasing renal and femoral blood flow in the dog and rabbit while lowering blood pressure,4 a characteristic not enjoyed by most other circulatory depressants. The drug is sympatholytic in some animals in that it antagonizes the pressor action of epinephrine5; that of hypertensin is also blocked.6-8 In man, nor-epinephrine may be partially opposed. There is suggestive evidence that the depressor effect occurs through action on the hind or mid-brain.4-6 Methyl and benzene substituted compounds appear to differ but little.4

In October, 1949, an investigation of the effects of chronic administration of C-5968 to renal hypertensive dogs was initiated. The drug was given intravenously in doses of 10 mg. every day or every other day. This regimen resulted in partial or complete control of hypertension without causing nitrogen retention, loss of weight, or other demonstrable toxic reactions.4

The characteristics of a true antihypertensive drug include the ability to lower blood pressure (a) without affecting the myocardium adversely, (b) without decreasing renal blood flow, and (c) without altering blood volume or viscosity. Because C-5968 appeared to have the pharmacologic properties of (a) and (b), was relatively nontoxic in dogs and rabbits, and could be administered by mouth, an investigation of its chronic therapeutic properties in hypertension has been conducted on 50 selected patients. This study was begun in September, 1949, and has been reported in abstract form elsewhere.9-11 The present report deals with the effects on blood pressure and other functions clinically measurable.

Methods

Fifty patients were selected from the wards of Barnes and St. Louis City Hospitals and from the Hypertension Clinic of Washington University. An attempt was made to obtain as many different types of hypertension as possible, both of the essential and malignant varieties, and those secondary to renal diseases. In hospital, blood pressures were recorded in the supine position at four-hourly intervals by members of the nursing staff; those of outpatients were measured once daily by the same physician at approximately the same hour, after

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5 to 10 minutes rest in the supine position and then immediately upon standing. The control periods varied widely; all hospitalized patients were observed at least one week prior to administration of the drug, and all measurements of blood pressure were recorded in the calculations. Outpatients usually had been followed for one to four years at intervals of two to three months. Placebos resembling the drug exactly were substituted for it without the patient’s knowledge unless there was no doubt that the effects observed were real and not psychogenic (in the more severe cases, for example). Hospitalized patients were not informed that the drug was given for hypertension.

All blood pressure measurements were considered to be “casual” in the sense that no concerted attempt was made to obtain “basal” readings. Therefore the results were evaluated by including the highest and lowest single values recorded and the averages of all made during the pretreatment period, the period of administration of the drug, that of administration of a placebo, and subsequent periods. This method of analysis, while severe, permitted comparisons of extremes as well as of means. Decline of average diastolic pressure of 20 mm. Hg or more from control values was considered a significant change.

1-Hydrizinophthalazine (C-5968) and a derivative, 4-methyl-1-hydrizinophthalazine (C-6130) were administered in doses of 50 to 150 mg. every four to six hours in hospitalized patients, and three to five times a day to outpatients. Variability of individual tolerance was encountered early in the study, the extremes of dosage being 75 to 900 mg. per day. No attempt was made to give more than 900 mg. All drugs were given by mouth.

The additive effect of the drug with other forms of therapy, such as lumbo-dorsal sympathectomy and restriction of sodium chloride, was evaluated in nine patients. Any regimen on which the patient had been placed was not changed during administration of the drug. In two instances Veriloid was used in conjunction with C-5968. No sedatives were employed.

There were several purposes for the present study. First, the antihypertensive properties of the drug and its limits were investigated. Relatively short periods of administration in hospital (10 to 30 days) were adequate to decide whether or not blood pressure could be maintained at lower levels without deleterious renal, cardiac or cerebral effects. Second, the toxicity and side action were evaluated. Third, the action following lumbo-dorsal sympathectomy and with other forms of therapy was studied, again requiring relatively short periods of observation. Fourth, a practical clinical experience with outpatients was obtained in order to assess long-term therapeutic possibilities; daily observations of a few patients for three to eight months were made.

**Results**

1. **Antihypertensive Properties.** Significant sustained lowering of diastolic pressure of 20 mm. Hg or more occurred during administration of 1-hydrizinophthalazine in 6 of 16 patients observed in hospital. All of these patients were suffering from uncomplicated arterial hypertension in the benign phase. In four the average change was more than 30 mm. Renal function as measured by the excretion of phenol red or the clearance of urea was not depressed. In no case were strictly normotenive levels maintained. In five other patients average diastolic pressure fell 15 mm. Hg or more.

![Basic structure of 1-hydrizinophthalazine](image)

Fig. 1. Basic structure of 1-hydrizinophthalazine. In C-5068, R is hydrogen; in C-6130, R is a methyl group. Other derivatives untested so far in hypertension include those in which R is a hydrazine group.

In malignant hypertension without nitrogen retention the drug appeared to have a more pronounced action than in severe benign hypertension. Given to three patients, it lowered diastolic pressure considerably, and these lower levels were maintained as long as it was given. Occasionally, relatively acute and severe depression was followed by what seemed to be tolerance, blood pressure then being maintained at levels lower than those of the control period but considerably higher than the lowest values reached. Malignant hypertension with uremia (six cases) was also remarkably susceptible to the action of the drug. In two instances patients who were mentally depressed became comatose as the blood pressure fell and in two others neurotic episodes developed.
The combined results are given in table 1. Albuminuria diminished or disappeared in 14 of 15 patients. Adverse electrocardiographic changes were not evident; paroxysmal nocturnal dyspnea was relieved in three patients without the use of digitalis. Regression of hemorrhages, exudates and papilledema in the ocular fundi occurred in four instances, but could not be attributed directly to the action of the drug. Little or no action was demonstrated in two patients with hypertension secondary to chronic glomerulonephritis and in three with congestive heart failure. In fact, blood pressure tended to rise in a case of the former, the only time an adverse effect was noticed.

2. Toxic Reactions. No serious chronic toxic manifestations were encountered in patients receiving 1-hydrazinophthalazine for periods of as long as eight months. These studies are continuing. Depression of red or white blood cells, evidence of renal damage, chronic gastrointestinal disturbances, or other severe manifestations were not seen. Careful studies of liver function were not made, as no patient presented symptoms suggestive of liver disorder. Electrocardiographic abnormalities were not found.

Side reactions to the drug were seen on first administration in 22 of 50 patients. Headache, of the type commonly experienced as a symptom of hypertension, was induced by the first

<table>
<thead>
<tr>
<th>Type of Hypertension</th>
<th>No. Cases</th>
<th>Fall of Average Diastolic Pressure mm. Hg</th>
<th>Albuminuria</th>
<th>P.S.P. Excretion in 15 minutes†</th>
<th>Time Administered No. Patients/Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>21-30</td>
<td>11-20</td>
<td>11</td>
</tr>
<tr>
<td>Hospital Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign Uncomplicated</td>
<td>16</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without N retention</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>With N retention</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Postsympathectomy</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>2</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>2</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Outpatients</td>
<td>15</td>
<td>9</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Benign Uncomplicated</td>
<td>12</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Postsympathectomy</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Totals</td>
<td>57*</td>
<td>13</td>
<td>22</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

* Seven cases were seen both in hospital and as outpatients.
† After intravenous injection.

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**TABLE 2.—Toxicity and Side Actions of C-5968 in Fifty Patients**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. Times Encountered</th>
<th>No. Times Disappeared On Continuing Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural Hypotension</td>
<td>45</td>
<td>38*</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Moderate</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral Symptoms</td>
<td>4</td>
<td>0†</td>
</tr>
</tbody>
</table>

* Became less but did not disappear.
† Disappeared in a few days on discontinuing drug.
few doses in 22 subjects, and was severe enough to cause discontinuance in four. The headache was frequently controlled by Dramamine. Raising the level of dosage appeared to cause headache to recur. If the drug was continued, the headache disappeared in all but four cases (table 2) within two to five days.

Tachycardia was common during the first few days, disappearing as the drug was continued. Postural hypotension, which might be marked at first, regressed considerably but remained during the administration. Nausea and vomiting were present in 11 cases, also disappearing in a day or two in nine.

When hypertension was severe, cerebral symptoms often accompanied the fall in blood pressure, usually disappearing later. These ranged from mild anxiety or depression, to acute anxiety states or severe depression and coma. They occurred in seven subjects, regressing in all but two who were severely uremic and who remained in coma.

3. Combined Action with Other Forms of Therapy. After lumbar dorsal sympathectomy 1-hydrazinophthalazine was found to exert a much more pronounced effect than before the operation. Seven patients were studied. Postural hypotension became so marked that dizziness in the upright position could readily be induced. The effects upon supine blood pressure were variable. During the month after operation, when the blood pressure had risen to relatively high values, normotensive levels could be continuously maintained in two subjects. In the remainder, who had had relatively unsuccessful sympathectomies one to four years previously, the effect was often considerable; standing blood pressure could be maintained at normal levels, although that in the supine position remained moderately elevated.

The drug was given to two patients who were on diets severely restricted as to salt. The results were quite favorable, and indicated increased susceptibility during salt restriction or rice diet. Veriloid was added to C-5968 in two cases; temporary but not sustained hypotensive levels were obtained. The combination of C-5968 with Priscoline or Regitine did not result in enhancement of the effect of either.

4. Clinical Trial on Outpatients. Fifteen patients suffering from benign arterial hypertension of various degrees of severity were given C-5968 or C-6130 for one to eight months; blood pressures, reclining and standing, were recorded six days a week. Placebos or no medication were given for short periods. Three patients refused the drug after three days because of headache, dizziness and faintness; all were in mild stages of the disease. Five others gave up the medication voluntarily after 2 to 10 weeks, usually because of the difficulty of making daily visits. Seven continued to accept treatment and three became dependent upon it. The results are shown in table 1 and figures 2 and 3.

The actions of C-5968 and C-6130 were compared in 10 subjects. No differences were detectable by these studies. Enteric coated tablets of the C-5968, given to six patients, either caused effects similar to those seen with ad-
Fig. 3. A. (Upper Chart) Effect of 1-hydrazinophthalazine in a 47 year old Negro woman with moderately severe benign hypertension of the endocrine type. Notations same as figure 2. Albuminuria of slight degree disappeared two weeks after therapy was begun but reappeared when it was stopped, only to disappear again on resumption of therapy. Renal function was not disturbed from low normal levels. Headache of moderate intensity disappeared. When minimal doses of Veriloid were given in addition, marked unsustained lowering of blood pressure occurred. Note the relatively small postural fall of systolic pressure and the rise of diastolic, indicated by the absence of shading. The control areas represent three years' observation.

B. (Lower Chart) Same in a 39 year old Negro woman with relatively mild hypertension. The postural systolic fall was greater, and lower levels were sustained which were sometimes at normal levels. Normal renal and cardiac function were unchanged. The control areas represent three years' observation.
administration of placebos or produced only minimal changes in blood pressure.

5. Comparative Effects in Different Types of Hypertension. Patients were classified according to methods and criteria previously described and the effects of the drug evaluated in each type. In general, it appeared that the most pronounced effects occurred in neurogenic hypertension, some cases of malignant hypertension and those who had had lumbodorsal sympathectomy; minimal changes were seen in severe renal hypertension with good renal function. A comparison of the relative effectiveness of C-5968 is shown in figures 4 to 8.

Discussion

The pharmacology of 1-hydrizinophthalazine and 4-methyl-1-hydrizinophthalazine is shown, in so far as is known, in table 3. It is obvious that these compounds have actions of a type not enjoyed by other known depressor agents. Evidence for a “sympatholytic” nature is equivocal and apparently dependent upon dosage and species. The site of action is not known; the blood pressure of “spinal” cats and dogs is not lowered by the drugs, suggesting an action on the vasomotor centers or hypothalamus. However, they may be considered autonomic blocking agents of a special and hitherto undescribed type, as evidenced by their ability to inhibit the pressor response to pain (cold pressor test) and to the Valsalva maneuver. The effects are not due to sedation, not due to direct action on smooth muscle, and are not primarily peripheral.

The action of these drugs on blood pressure and renal blood flow are of paramount importance to the problem of hypertension. Any substance which lowers blood pressure without causing diminution of renal blood flow is of interest. The present drugs apparently exhibit just this action. Being relatively nontoxic, they can be administered for several months to patients suffering from arterial hypertension of certain types and varieties with the expectation that the blood pressure will be lowered without deleterious renal effects. It can be assumed that thereby some of the damage to the cardiovascular system resulting from sustained high arterial pressure may be partially prevented.

There is little evidence, however, that the present investigation represents much more than a therapeutic tour de force. Convincing data that life was prolonged by the drug was present in only two patients in whom considerably diminished renal function, severe retinitis, and severe hypertension all regressed remarkably after two to three months’ treatment. Several years of continuous therapy in a large number of patients may be necessary to evaluate long-term benefits, if any.

Although no chronic toxic manifestations were observed, undoubtedly some will appear with wider use of these drugs. It will then be
FIG. 5. Effect of 1-hydrazinophthalazine in neurogenic hypertension. The bars represent the extremes of systolic and diastolic pressure, the horizontal lines through them the means. The cross-hatched bars indicate the control periods, and include all measurements recorded up to four years prior to therapy. The solid bars indicate the periods of treatment, and the open bars those during which a placebo or no medication was given subsequent to treatment. The numbers show the number of days of therapy from which the blood pressure measurements were taken; a plus sign indicates outpatients. (S) after the initials in the bottom row means that the patient has had lumbo-dorsal sympathectomy. All measurements were made in the supine position. Note the relatively good response in most of the members of this group, except D.B. and E.B.

FIG. 6. Effect of 1-hydrazinophthalazine in malignant hypertension. Notations same as figure 5. The X above the initials indicates that the patient died during observation. Note the relatively good response in this group, with the exception of A.H., who died of a cerebral hemorrhage during treatment; his blood pressure while standing was controlled at normal levels, but when supine it remained high. All measurements were made in the supine position in hospital.
necessary to assess them against possible therapeutic value. In almost every case foreign unnatural chemicals introduced into the human body have resulted in toxic reactions. Evidence for this drug resembling a naturally occurring substance is lacking.

The side actions of these drugs are usually not serious enough to contraindicate a therapeutic trial. The headache, which may be severe, is probably not due to direct action of the drugs, but may be an indirect result of the lowered blood pressure and may be caused by the release of histamine. Typical headaches can be induced both by the drugs and by histamine, may be accompanied by stuffiness of the nose, watering of the eyes, and injection of the conjunctivae and can often be relieved by antihistaminic agents. The fact that they usually disappear while the drugs are being given is good evidence against their being drug-induced. Tachycardia and postural hypotension may also diminish as blood pressure becomes stabilized at lower levels, although the latter usually persists in mild degree; these are probably direct actions of the drugs. Nausea, vomiting and the occasional abdominal cramps and desire for defecation experienced by a few individuals may represent signs of autonomic imbalance induced by the drugs, especially as their symptoms were seen more often in patients who had been subjected to sympathec-
malignant hypertension, it is our practice to initiate therapy slowly, with gradually increasing doses, preferably in hospital or, at the very least, under daily observation.

These two members of the hydrazinophthalazine group are the most effective agents against hypertension so far encountered for practical clinical use and represent true antihypertensive drugs. They do not, however, provide a therapeutic answer to this pressing problem; their effects are only partial. Only insofar as they may lead to further developments along the present line which will be considerably more effective shall the present study prove valuable. The treatment of renal hypertension remains unsolved.

**Summary and Conclusions**

Fifty patients suffering from arterial hypertension of various types were given 1-hydrazinophthalazine and/or 4-methyl-1-hydrazinophthalazine by mouth for periods of 1 to 40 weeks. Significant lowering of average diastolic blood pressure of 20 mm. Hg or more resulted in 35 instances, but in only a few of the mildest cases were normotensive levels sustained. The changes were not accompanied by deleterious effects upon kidneys or heart. These agents therefore represent true antihypertensive drugs of moderate potency.

**Acknowledgment**

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ADDENDUM

Experience with this agent in an additional 20 patients has confirmed the present observations. No other evidences of chronic toxicity have appeared. In three cases, high fever without evidence of infection developed during administration of C-5968, regressing spontaneously; two of these patients had shown signs of previous cerebral damage. The fever was believed to be of central origin. Patients receiving this drug continuously for as long as 11 months have shown no signs of toxicity; blood counts and studies of liver function have remained normal. Tolerance to the drug has developed in several instances; discontinuance for a few days has restored susceptibility.

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