Clinical Trial of Ilidar, a New Dibenzazepine Adrenergic Blocking Drug, in the Treatment of Peripheral Vascular Diseases and Miscellaneous Complaints

By Harold D. Green, M.D., and Hugh H. DuBose, M.D.

Ilidar, a new adrenergic blocking drug, has been administered to 116 patients; follow-up was adequate on 86. The drug was highly effective in patients with predominantly vasospastic disorders and in patients with postphlebitic syndrome, and moderately effective in patients with thromboangiitis and arteriosclerosis. Most patients could tolerate 50 to 75 mg. three to four times a day. Side effects were principally those to be expected from the moderate postural hypotension associated with effective sympathetic blockade, namely, weakness, dizziness, nausea.

This paper reports the results of the initial clinical trial of Ilidar, a new adrenergic blocking drug. This drug, originally designated as Ro 2-3248, is one of a new group of dibenzazepine derivatives first described by Wenner. Many of these, the most potent being Ilidar, were shown to be epinephrine antagonists by Randall and Smith. Moore, Richardson and Green found Ilidar to be a prompt, moderately long acting vasodilator when injected intra-arterially in the normally innervated hind limb of dogs. The normal vasoconstrictor response to epinephrine was found to be reversed following intra-arterial Ilidar; this reversal of response persisted in the different experiments for periods of time varying from 1 hour, 17 minutes to 5 hours, 36 minutes. The normal vasoconstrictor response to epinephrine was blocked for a considerably longer period. Tachyphylaxis did not develop with repeated injections; and doses of Ilidar up to 16 mg. per kilogram of body weight, given as intravenous infusions to anesthetized dogs over a half hour period, caused no fatalities in this study.

Ilidar blocks the vasoconstrictor responses to epinephrine, to norepinephrine and to sympathetic nerve impulses in skeletal muscle. In skeletal muscle Ilidar unmasks a latent dilator response to epinephrine, that is, converts the constrictor response to vasodilatation. This epinephrine reversal is induced at a lower dose of Ilidar than that required to block the other adrenergic vasoconstrictor responses in skeletal muscle or to block all adrenergic vasoconstrictor responses in skin. Ilidar is temporarily stored in fatty tissue and is eliminated by metabolism; only about 5 percent appears in the urine.

It is well known that the element of vasospasm plays a role in every type of peripheral vascular disease, varying from the tremendous degree present in Raynaud's syndrome to the smaller but definitely demonstrable degree complicating most cases of arteriosclerosis obliterans. Any drug which might be capable of relaxing this vasospasm should be beneficial in these conditions.

Since Ilidar has proved in animal experimentation to be a safe, potent, adrenergic blocking drug capable of relaxing vasospasm due to sympathetic activity, it was felt that a clinical trial of this drug was warranted, with the aim of establishing therapeutically effective
dose levels, maximum tolerated doses, anticipated side reactions and possible therapeutic potentialities.

METHODS

Initial studies with Ilidar* were carried out on 10 healthy medical students. The drug was administered intravenously over a half-hour period in a dose of 1.0 mg per kilogram of body weight. These studies were carried out in a constant temperature room, utilizing copper-constantin thermocouples for skin temperature recordings as previously described.10

After these initial studies 73 patients were subjected to temperature studies during which Ilidar was administered intravenously in amounts of 1 mg. per kilogram over the course of one-half to one hour to demonstrate the degree, if any, of vasospastic element present, and thus to predict the probable effectiveness of the drug.

At the time this analysis was begun, 116 patients with various forms of peripheral vascular disorders had been started on oral Ilidar with instructions to increase gradually the dose as tolerated up to four or more such tablets four times a day. The instructions warned the patient not to increase the dose if any side reaction such as dizziness, nausea or vomiting, took place but to drop back to the largest tolerated dose.

During the first part of the study tablets containing 25 or 50 mg. of Ilidar hydrochloride were used; for all of the latter part of the study tablets of 30 or 60 mg. of Ilidar phosphate were used. Both the 25 mg. Ilidar hydrochloride and the 30 mg. Ilidar phosphate tablets contain an equivalent amount of Ilidar base. In order to simplify presentation, we have expressed the results throughout as multiples of the 25 mg. tablets. Ilidar phosphate is less hygroscopic and therefore permits a more stable tablet than the hydrochloride.

RESULTS AND DISCUSSION

A. Control Studies on Normal Subjects

All of the 10 normal subjects showed fairly good vasodilation in the upper extremities and moderately good vasodilation in the lower extremities in response to the intravenous infusion of 1 mg. per kilogram of Ilidar when given without associated body warming. None had any significant side effects or any significant fall in arterial blood pressure.

* The Ilidar was kindly supplied by Dr. Elmer Sevrinhaus of Hoffmann-LaRoche, Inc., Nutley, N. J. The injectible preparation was a clear, colorless solution with a pH of 6.0, ± 0.1 pH unit, and contained 10 mg. per milliliter of Ilidar phosphate.

B. Results of Intravenous Infusions of Ilidar in Patients

In only 4 of the 73 patients tested in the constant temperature room did the intravenous infusion have to be discontinued because of adverse side reactions. Two of these four patients developed moderate hypotension, one developed nausea and dizziness and the fourth became weak and restless. Fifty-nine of the 73 patients had good to excellent responses, six had no response and the remainder minimal or fair responses. There were several patients in whom oblitative disease was localized to or was more advanced in one extremity. This extremity was likely to show no response while the other extremity showed a good response. Many patients received only a part of the standard 1 mg. per kilogram intravenous dose because they obtained a maximum response prior to completion of the infusion which was discontinued in this event.

C. Categories of Patients Receiving Oral Ilidar

Eighty-six of the original 116 patients were followed closely enough to allow us to attempt to draw certain conclusions including tolerated dose range, therapeutically effective dose range and untoward side effects. These patients were divided into diagnostic categories as shown in table 1.

In order to determine if the age of the patient played any demonstrable role in the tolerance of the drug or its effectiveness, the patients were also divided into arbitrarily selected age groups of 18 to 40 years, 41 to 60 years, and 61 to 79 years. Table 2 divides each of the three arbitrarily selected age groups into three

<table>
<thead>
<tr>
<th>Table 1.—Distribution of Patients Treated with Ilidar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total started on drug .................. 116</td>
</tr>
<tr>
<td>Total followed .................. 86</td>
</tr>
<tr>
<td>Breakdown of patients followed</td>
</tr>
<tr>
<td>Arteriosclerotics .................. 29</td>
</tr>
<tr>
<td>Sudden arterial occlusion .......... 4</td>
</tr>
<tr>
<td>Thromboangitis obliterans .......... 8</td>
</tr>
<tr>
<td>Raynaud's .................. 7</td>
</tr>
<tr>
<td>Postphlebitic syndrome .......... 10</td>
</tr>
<tr>
<td>Miscellaneous .................. 28</td>
</tr>
</tbody>
</table>
## Table 2—Tabulation of Tolerated Doses and Doses Producing Side Effects in Eighty-six Patients Treated with Lidar

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. of Patients</th>
<th>A. Patients Experiencing No Side Effects with Lidar</th>
<th>B. Patients Who Experienced Side Effects with Lowest Dose Given and Stopped Drug</th>
<th>C. Patients Able to Tolerate Average Doses of Lidar but Who Were Pushed to Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-40</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-60</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61-79</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- **AS** = arteriosclerosis
- **M** = miscellaneous
- **PP** = postphlebitic syndrome
- **R** = Raynaud's
- **SAO** = sudden arterial occlusion
- **TAO** = thromboangiitis obliterans
categories based on tolerance of the drug: (A) those who did not experience side reactions with the maximum dose taken, (B) those patients who developed side effects with the lowest dose taken, and (C) those who could tolerate the indicated dose but developed side effects when pushed to larger doses. The duration of the medication is also recorded in the tables. This time ranged from 1 week to 15 months. Three of the patients took the drug for more than one year, 17 were on Ildar continuously for 6 to 12 months and 16 for 3 to 6 months. No evidence of cumulative effect was demonstrated.

D. Hemograms on Patients Receiving Oral Ildar

All of the patients taking the drug received initial hemograms and were followed carefully from a hematologic aspect with frequent determinations of the hemoglobin, total white blood cell count and differential count. In some of the patients, if the platelet count did not appear adequate on the stained smear, platelet counts were done. No case was there any evidence of depression of bone marrow activity.

E. Side Reactions in Patients Receiving Minimal Oral Doses of Ildar

Eight of the 86 patients, on whom we had adequate follow up, experienced side reactions of sufficient severity that the patient discontinued the drug (see table 2B).

(1) Febrile Reactions. One of these (2AS) had chills, fever and nausea while taking 25 mg. three times a day; the fever began two to three hours after taking a dose of Ildar. The drug was stopped, but a few days later the patient took one 25 mg. tablet and the fever recurred. After several more days another 25 mg. tablet was taken and again the fever recurred. This reaction was interpreted as drug fever.*

* Since this analysis was begun we have started 85 additional patients (total 201 patients) on oral Ildar. Among this group two patients developed a febrile reaction within two and three hours after an oral dose of Ildar. Further medication with Ildar was not given to one. The other consented to take one 25 mg. tablet two more times on different days and had a chill, fever and nausea lasting a few hours after each dose. All three of the patients experiencing

(2) Gastrointestinal Disturbances. Two patients, (9AS, 11AS) developed severe nausea and vomiting while taking 50 mg. twice a day and four times a day, respectively, which precluded further use of the medication. Since one of these (9AS) had taken the drug for two months the reaction may well have been due to something other than the drug.

(3) Postural Hypotension. Two patients developed severe postural hypotension (8M, 23AS). In one of these (23AS) this response directly resulted from failure of the patient to obey instructions in that he proceeded to a higher dose of the medication (75 mg.) even though he experienced mild side effects (dizziness) while taking 50 mg. four times a day. This patient continued to have severe postural hypotension for eight or nine days after discontinuing the drug. In the other patient experiencing severe hypotension, it was not established definitely whether he had experienced milder reactions with initial doses and had proceeded against instructions to the next higher dose but it seems likely that he did.

(4) Miscellaneous Symptoms. Another of the patients (6AS) in this group developed weakness, nausea, vomiting, triple vision, headaches, and syncope after taking doses of 50 mg. four times a day for one month. This patient was also receiving digitalis and quinidine at the same time so it was never clear whether Ildar was actually playing a role in the production of these symptoms. Since Ildar in this study has not shown any tendency to an accumulative effect in the dose range used, it seems unlikely that this patient would develop symptoms after being on the drug three or four weeks.

The two remaining patients (2PP, 4M) placed in this group discontinued the drug of their own volition even though the side effects experienced were only mild. Each was taking 50 mg. per dose. One complained of "a washed
out feeling" and the other of "slight dizziness" for a short time after each dose.

In summary: only 1 out of 86 patients (2AS) definitely could not tolerate the drug in minimal doses of 25 mg.

F. Side Reactions in Patients Receiving Maximum Tolerated Doses

In the patients purposely pushed to tolerance, the great majority of the symptoms experienced were dizziness, nausea, and weakness with an occasional patient complaining of drowsiness (see table 2C). In most of the instances, nausea could be eliminated by taking the medication after meals rather than before. The original instruction given to each patient requested that the medication be taken before meals, for it was felt that the maximum response as well as maximum detection of side reactions could best be obtained in this manner. The dizziness in most cases would pass off if the patient would lie down for a few minutes. In one or two of the patients the symptom complex of nervousness, weakness, palpitation and sweating suggested hypoglycemic reactions and in one of these cases the symptoms seemed to be alleviated by the ingestion of food.

Diarrhea occurred in three patients. In each case it occurred after the patient had been taking the drug for at least two months, and in each case the diarrhea stopped several days after the drug was discontinued. However paregoric and other antidiarrheal compounds were prescribed by the patients' local physician. In no case could the diarrhea be attributed definitely to Ilidar, but in no instance could it be eliminated as the offending agent.

Two patients had reactivation of previously diagnosed peptic ulcers. A causal relation could not be postulated definitely in these cases.

Several of the patients with weakness and drowsiness seemed to become tolerant of the dose producing these symptoms after several days of the medication and no longer experienced any further unpleasant side reactions. However, these patients were included in table 2C under those experiencing side reactions.

As seen from table 3, many of the symptoms listed occurred only in one patient. In practically no case could these isolated symptoms be attributed definitely to Ilidar. The majority of the symptoms occurred in the miscellaneous group of patients, many of whom had multiple complaints prior to medication and were difficult to evaluate from this standpoint.

In only one instance did the medication seem to aggravate the pre-existing symptoms for which the drug was given. This was in an elderly man with arteriosclerosis obliterans who complained of a severe intensification of the

<table>
<thead>
<tr>
<th>Symptom</th>
<th>18-40</th>
<th>41-60</th>
<th>60-79</th>
<th>18-40</th>
<th>41-60</th>
<th>61-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness*</td>
<td>0</td>
<td>6</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Nausea†</td>
<td>9</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope‡</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea§</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning skin</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple vision</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trembly</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug fever</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precordial pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deafness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair standing on end</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritis (? hives)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous voiding</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flashes</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Dizziness, relieved by lying down in majority of cases.
† Nausea occurred only if drug taken on empty stomach in majority of cases.
‡ Syncope associated on two occasions with severe postural hypotension.
§ In every case in which diarrhea occurred, it was only after patient had been on continuous therapy for at least two months, so etiology always in doubt.
burning sensation in his legs while on Ildidar. He was relieved by stopping the drug.

G. Summary of Tolerated Doses.

During most of the study 25 mg. tablets were available. The analysis of doses were complicated, however, by the fact that during part of the study the smallest available tablet was 50 mg. Of the total of 86 patients, 41 voluntarily increased the dose progressively to tolerance, and 45 did not increase the dose to the point where they experienced side effects.

(1) Initial Test Doses. All patients took an initial single test dose of 25 or 50 mg. without side effects.

(2) Repeated Doses of 25 mg. (75 to 100 mg. per Day). Two of the 86 patients (8M, 2AS) in this series developed hypotension or drug fever on repeated doses of 25 mg., and discontinued the drug. Two patients (8TAO, 9M) tried single doses and one repeated doses of 50 mg. but developed side effects. They dropped back to 25 mg. which they were able to take without symptoms. One patient (25M) did not try larger doses. Six patients who started initially on repeated doses of 50 mg. (the smallest tablet then available) developed side effects and stopped taking the drug. They are included in paragraph (3) below, but since they did not try 25 mg. they are not included in the analysis of the 25 mg. dose. The remaining patients tolerated well this and larger doses. Thus, 97 per cent (78 out of 80) tolerated repeated doses of 25 mg. or more without side effects; and 2 per cent (2 of 86) could not tolerate repeated 25 mg. doses.

(3) Repeated Doses of 50 mg. (150 to 200 mg. per Day). Of the 86 patients 83 tried one or more 50 mg. doses. Nine of the 83 experienced dizziness, nausea, weakness, vomiting, hypotension, burning of the skin or cutis anserina; six of the nine stopped the drug (2PP, 11AS, 6AS, 9AS, 23AS, 4M), three dropped back and continued satisfactorily with 25 mg. doses (8TAO, 9M, 2TAO). One patient (16AS) tolerated 50 mg. three times a day, but experienced precordial pain, weakness, and dizziness whenever he tried to increase the dose to 50 mg. four times a day. Ten patients did not attempt to increase the dose. Four patients (4R, 6R, 18M, 7M) developed side effects at 75 mg. doses and dropped back to 50 mg. doses and nine patients (17M, 5R, 28M, 6TAO, 1TAO, 4AS, 10PP, 23M, 3AS) tried 100 mg. and dropped back to 50 mg. doses which they were able to tolerate without side effects. The remaining 50 tolerated larger doses. Thus 86 per cent (74 out of 86) could tolerate repeated doses of 50 mg. or larger and 13 per cent (11 of 86) experienced side effects with 50 mg. or less three to four times a day.

(4) Repeated Doses of 75 mg. (225 to 300 mg. per Day). Of the 63 patients who tried doses larger than 50 mg., 54 tried one or more doses of 75 mg. and nine skipped the 75 mg. dose and tried 100 mg. doses, since 25 mg. tablets were not available to them. Of the 54 who tried one or more 75 mg. doses, four experienced orthostatic dizziness, blacking out and reduced hearing and weakness and trembling relieved by eating (4R, 6R, 18M, 7M). All four dropped back to and continued satisfactorily at repeated doses of 50 mg. Four (11M, 6M, 17AS, 24AS) of the eight who did not experience side effects at 75 mg. per dose, did not increase the dose further; five of the 9 patients (10M, 26AS, 3TAO, 15AS, 1AS) tried repeated doses of 100 mg. and dropped back to 75 mg. because of side effects at the larger doses. Forty-one patients tolerated repeated doses larger than 75 mg. Thus 58 per cent (50 of 86) could tolerate doses of 75 mg. or more without side effects and 17 per cent (15 of 86) experienced side effects with doses of 75 mg. or less three to four times a day.

(5) Repeated Doses of 100 mg. (300 to 400 mg. per Day). Of the 86 patients, 55 tried one or more doses of 100 mg. Fourteen of these experienced dizziness, nausea, weakness, nasal stuffiness, diarrhea, headache, urticaria, pruritus, hot flashes, or drowsiness or were irritable and nervous; nine of these (17M, 5R, 28M, 6TAO, 1TAO, 4AS, 10PP, 23M, 3AS) dropped back to 50 mg. doses, and five (10M, 26AS, 3TAO, 15AS, 1AS) dropped back to 75 mg. doses which they could tolerate. Seventeen patients did not try to increase the dose above 100 mg. Five (5M, 10AS, 22AS, 8AS, 5AS) tried to increase the dose to 125 mg. and two (4TAO, 7TAO) tried to increase the dose to
150 mg; but, because of side effects, these seven patients dropped back to repeated doses of 100 mg. Seventeen patients tolerated larger doses. Thus 48 per cent (41 of 86) could tolerate repeated doses of 100 mg, or larger and 34 per cent (29 of 86) experienced side effects at doses of 100 mg, or less three to four times a day.

(6) Repeated Doses of 125 mg. (375 to 500 mg, per Day). Twenty-two patients tried repeated doses of 125 mg.; five of these (5M, 10AS, 22AS, 8AS, 5AS) experienced dizziness, nausea on an empty stomach, loss of energy, and nervousness, and dropped back to 100 mg. which they took without side effects. One (16M) did not increase the dose further, four (13M, 13AS, 28AS, 3SAO) tried doses of 150 mg. but experienced side effects so dropped back to 125 mg., and 12 tolerated larger doses. Thus 20 per cent (17 of 86) could tolerate repeated doses of 125 mg. or larger, and 40 per cent (34 of 86) experienced side effects at repeated doses of 125 mg. or less, three to four times a day.

(7) Repeated Doses of 150 mg. (450 to 600 mg, per Day). Eighteen patients tried repeated doses of 150 mg. Six of these experienced dizziness, weakness, sluggishness, palpitation, sweating, tinnitus, blurred vision and colic. Four of them (13M, 13AS, 28AS, 3SAO) dropped back to 125 mg. and two (4TAO, 7TAO) dropped back to 100 mg. doses which they took without side effects. Nine patients did not try to increase the dose further; one of these (2R), however, took the 150 mg. dose six times a day for a daily dose of 900 mg. Three (3PP, 2M, 18AS, 12AS, 19AS, 14AS) took 150 mg. four times a day. Thus 12 per cent (10 of 86) could tolerate total daily doses of 600 mg. or larger.

(8) Repeated Doses of 200 mg. (600 to 800 mg, per Day). Three patients (5TAO, 6PP, 5PP) (3 per cent) took repeated doses of 200 mg. without side effects. From group (7) above, one patient (2R), took 150 mg. six times a day and six more (3PP, 2M, 18AS, 12AS, 19AS, 14AS) took 150 mg. four times a day. Thus 12 per cent (10 of 86) could tolerate total daily doses of 600 mg. or larger.

(9) Relationship of Age to Tolerance. It is apparent from table 4 that the average daily tolerated dose is in the range of 300 mg. divided into three or four doses. As shown in tables 2 and 4, there is no significant difference in the tolerance of the drug in the three age groups nor is there any significant difference in the doses producing side effects in the three groups.

II. Therapeutic Dose Range

The total daily dose in patients benefitted from the drug ranged from 50 mg. to 900 mg. per day. In general, improvement seemed to increase in proportion to the total dosage but there was a good bit of individual variation in this regard. On the basis of these studies, it is
not felt that any great benefits are derived in exceeding a dose corresponding to repeated
doses of 75 to 100 mg. (total daily doses of
225 to 400 mg.).

I. Therapeutic Impressions

The chief interest in this initial clinical trial
with Ilidar was to investigate and establish its
tolerated dose, side reactions and untoward
complications. In regard to therapeutic re-
sponse no controlled series was run and in only
a few patients was Ilidar used alone. Therefore
only an impression as to the therapeutic
effectiveness of Ilidar can be gained from the
patients studied thus far. Simultaneous therapy
of one kind or another was used in most pa-
tients. Many of the arteriosclerotics were
receiving low fat diet, lipotropic agents, B₃,
thiamine, sedation, analgesia and the usual
instructions to walk slower and discontinue
tobacco. Many of the patients with edema were
given elastic stockings and those with stasis
dermatitis and ulcerations received local skin
therapy. Many were put on weight reduction
diets, modified activity with rest periods of
leg elevation, and similar regimens, all tending
to relieve symptoms. Therefore, except for
several patients with Raynaud’s syndrome and
one or two in each of the other groups as men-
tioned below, any beneficial results cannot be
attributed to any one therapeutic agent. The
majority of the patients included in the mis-
cellaneous group received only Ilidar.

1. Arteriosclerosis Obliterans. Of the 29
patients classified as having arteriosclerosis
obliterans, about 10 or 31 per cent obtained
some symptomatic benefit while using Ilidar.
The complaint of intermittent claudication was
uniformly unrelieved. The symptoms of aching,
burning, coldness, night cramps and numbness
seemed to respond best to Ilidar. There was no
uniform evidence of objective improvement in
these patients as measured by the treadmill
tolerance test. Five of those showing no benefit
were patients who experienced side effects with
minimal doses of 25 mg. to 50 mg.

2. Sudden Arterial Occlusion. Three of the
group of four patients having classical signs and
symptoms of sudden arterial occlusion were 56
years of age or older and the occlusions were
thought to be due to thrombosis secondary to
arteriosclerosis. The fourth was a 29 year old
male with sudden occlusion of the left popliteal
artery with no apparent cause for thrombosis
or embolism. Two of these patients obtained
partial relief of symptoms which included
numbness, pain and coldness, but exercise
capacity improved in only one who gradually
obtained complete relief from intermittent
claudication over a two month period while
taking Ilidar. None of these patients were
seen in the first few days following their appar-
ent sudden arterial occlusion. Amputation was
not necessary in any of these patients.

3. Thromboangiitis Obliterans. Five of a
group of eight patients with thromboangiitis
obliterans experienced subjective improvement
while taking Ilidar. The symptoms of coldness,
aching and burning responded most often and
most satisfactorily. Two patients observed a
moderate improvement in claudication. These
two patients had good responses to the intra-
venous test. This improvement continued in
one even though the drug was stopped. The
other noted a return of all symptoms during a
trial period off the drug with recurrence of
beneficial effect after restarting the drug. In
the cases of thromboangiitis obliterans, there
seemed to be no correlation between the dose
and the benefit obtained.

4. Raynaud’s Syndrome. Seven patients with
vasospastic disease (Raynaud’s syndrome)
were treated with Ilidar. Five of these or about
70 per cent obtained beneficial results. Two of
these experienced rapid, complete relief of
symptoms including cold, painful, blanched
and swollen fingers. One of these patients who
obtained complete relief had been troubled for
four years with severe symptoms that appar-
ently followed an electrical burn. Two patients
received no benefit whatsoever. It is interesting
that both of these patients obtained excellent
responses to the intravenous test but could
tolerate only the relatively small oral doses of
50 mg. three times a day. The five patients who
did benefit were able to tolerate larger doses
than the two who did not respond.

5. Postphlebitic Syndrome. Eighty per cent of
a group of 10 patients diagnosed as postphle-
bitic syndrome showed improvement on Ilidar.
These patients had edema, tender red areas along the course of veins, stasis dermatitis and superficial ulcerations, tightness in the calves and one had intermittent claudication. In those benefitted there was moderate to complete relief of symptoms including claudication in the one instance; and objectively there was definite reduction in stasis edema, improvement of the associated dermitis and healing of the stasis ulcer cases. One of the two that failed to benefit was unable to tolerate the drug and discontinued its use after three days on small doses.

(6) Miscellaneous. A group of 28 patients were classified as miscellaneous. Ten of these seemed to benefit symptomatically from Ilidar. Five of these had evidence from temperature studies of increased vasospasm in the lower extremities and occasionally the upper extremities. These patients complained of coldness of the extremities, aching in calves and burning of the feet. All of the symptoms were aggravated during cold weather and several of this group found they needed to take Ilidar only during the colder months as they remained asymptomatic without medication during the summer. At least one of these patients is starting his second winter since being started on Ilidar and after being free of symptoms all summer, is finding it necessary to take Ilidar again and is obtaining marked symptomatic relief.

Two patients with paravertebral muscle spasm and pain associated with osteoarthritis of the spine reported they gained complete relief of symptoms after starting Ilidar. The benefit continued after the drug was discontinued. Two or three patients diagnosed as causalgia also obtained symptomatic relief.

The most dramatic response in the entire series was that of a 32 year old male diagnosed as acrosclerosis. He had noted stiff, painful fingers for the past nine months and was unable to close his hands when first seen. After two weeks of Ilidar, during which time the only other therapy consisted in the avoidance of tobacco, he showed remarkable improvement and was able to play golf for the first time in seven months.

Summary and Conclusions

This study describes our clinical experiences with Ilidar, a new adrenergic blocking agent.

An initial study was carried out using 10 normal medical students who received intravenous infusions of Ilidar while in a constant temperature room where continuous skin temperatures were recorded. In all 10 satisfactory relaxation of cold induced vasoconstriction was obtained, and no significant side effects were noted.

Seventy-three patients were subjected to a similar intravenous test. A marked vasodilating effect was noted in all but 14 who had moderate to advanced obliterative arterial disease. Sixty-nine of the 73 tolerated the drug without significant side effects.

One hundred sixteen patients, most of whom had some form of peripheral vascular disorder involving a vasospastic component, were treated with oral Ilidar. Follow up was adequate on 86 of these patients.

In this study the Ilidar was well tolerated, in therapeutically effective oral doses, by 74 of the 86 patients. Only 1 of 86 individuals could not tolerate the drug in any amount. Drug fever and severe nausea and vomiting were the manifestations of these apparent idiosyncrasies.

In 33 of the patients the dose was increased progressively until side effects were experienced. Those most commonly noted were dizziness, nausea, weakness, syncope and drowsiness. Eighty-six per cent of the patients tolerated 150 to 200 mg. a day; 58 per cent tolerated 225 to 300 mg. a day, and 34 per cent tolerated 300 to 400 mg. a day given in three or four divided doses a day. From these observations it is concluded that, for the majority of patients the oral medication should be in the range of 50 to 75 mg. three or four times daily, though in a fair number of patients dosage can be pushed to higher levels if necessary.

No apparent long-time cumulative effect of the medication and no bone marrow depression were noted in the 36 patients who took the drug continuously from 3 to 15 months.

The mildness and infrequency of the side reactions make Ilidar one of the most pleasant drugs in its class to use. However, the mildness of the reactions may constitute one of its
greatest hazards in that it may allow an occasional patient to reach a dosage which results in a high degree of sympathetic blockade and possibly in serious hypotensive episodes without the preliminary warning of less serious toxic manifestations. Careful patient instruction should, however, virtually eliminate this possibility.

The drug proved highly effective in patients with predominantly vasospastic disorders as manifest by coldness, blanching and aching of the extremities, especially when aggravated by cold weather. Healing of superficial ulceration was noted in several of this group. Relief was experienced by several patients with vague symptoms suggestive of myalgia. Significant benefit was noted in patients with the postphlebitic syndrome when used in conjunction with supportive therapy. Subjective improvement was noted in five of eight patients with thromboangiitis obliterans and in 34 per cent of 29 patients classified as having arteriosclerosis obliterans, and in three of four patients who had experienced sudden arterial occlusion.

**Sumario Español**

"Ildar," un nuevo agente bloqueador adrenérgico, ha sido administrado a 116 pacientes; observación continua fué adecuada en 86. La droga fué altamente eficaz en pacientes con desordenes predominantemente vasoespásticos y en pacientes con síndromes postflebiticos y moderadamente efectiva en pacientes con tromboangiitis y arteriosclerosis. La mayor parte de los pacientes pudo tolerar de 50 a 75 mg. tres o cuatro veces al día. Los efectos no deseados fueron principalmente aquellos que se esperaban de la moderada hipotensión postural asociada con un bloqueo simpático efectivo, o sean, debilidad, mareos y nauseas.

**REFERENCES**


3. **Moore, P. E., Richardson A. W., and Green, H. D.:** Effects of a new dibenzazepine derivative Ro 2-3248, 6-allyl-6,7-dihydro-5H-dibenz [c, e] azepine phosphate, upon the blood flow, the peripheral resistance and the response to injections of epinephrine of the innervated hind limb of the dog. J. Pharmacol Exper. Therap. 106: 14, 1952.

4. **Lanier, J. T., Green, H. D., Hardaway, J., Johnson, H. D., and Donald, W. B.:** Fundamental difference in the reactivity of the blood vessels in skin compared with those in muscle. Blood flow response in these two beds to ischaemia, and to intra-arterial injections of methacholine, epinephrine and noradrenaline before and after administration of antiadrenergic drugs. Circulation Research 1: 40, 1953.

5. **Johnson, H. D., Green, H. D., and Lanier, J. T.:** Comparison of adrenergic blocking action of Ildar (Ro 2-3248), Regitine (C-7337) and Priscoline in the innervated saphenous arterial bed (skin exclusive of muscle) and femoral arterial bed (muscle exclusive of skin) of the anesthetized dog. J. Pharmacol. Exper. Therap. 108: 144, 1955.


9. **Randall, L. O.:** Personal communication. Hoffmann-LaRoche, Inc.

Clinical Trial of Ildar, a New Dibenzazepine Adrenergic Blocking Drug, in the Treatment of Peripheral Vascular Diseases and Miscellaneous Complaints

HAROLD D. GREEN and HUGH H. DUBOSE

Circulation. 1954;10:374-383
doi: 10.1161/01.CIR.10.3.374

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1954 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/10/3/374

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/