Effect of Dibenzyline on Skin Temperature, Peripheral Blood Flow, and Vasomotor Responses in Normal Patients and Patients with Increased Vasoconstrictor Tone


Dibenzyline is an orally effective, moderately potent, long acting, adrenergic blocking agent. The drug is capable of at least partially preventing the vasoconstrictor responses to cold and to injected Neosynephrine. Blood flow and temperature responses to this agent do not always parallel results obtained following surgical sympathectomy, but the degree of effect appears to be sufficient to produce a clinical response. Side effects and the development of “tolerance” may limit the use of Dibenzyline in clinical medicine.

Several reports have appeared during the past year confirming the observation that Dibenzyline (SKF 688A) is a specific sympathetic blocking agent.1-3 It is similar in action to Dibenamine, but is more potent, less toxic and is orally effective. The clinical usefulness of the drug has not been completely established. There is evidence to support its usefulness in the treatment of some peripheral diseases,4, 5 a limited group of hypertensive patients,6 and in patients with pheochromocytoma.7 Some observers have obtained a blockade of the pressor response to cold or intravenous Neosynephrine with oral Dibenzyline in both normotensive and hypertensive individuals.3, 4, 6 Others have failed to note a significant change in blood flow or vasomotor responses after oral medication.8 Woodward, Hoobler, and Nickerson, however, obtained marked increases in foot blood flow following intravenous administration of Dibenzyline at room temperatures.9

It is the purpose of this report to summarize our findings in a group of normal patients and patients with normal blood pressure but evidence of increased vasoconstrictor tone who were given single or multiple blocking doses of oral, intravenous, or intra-arterial Dibenzyline.* Subcutaneous or intramuscular administration was not used because of the possibility of producing local tissue necrosis. Results of long-term administration and comparative studies with Priscoline, penta-, and hexamethonium will be published elsewhere.5, 10

Materials and Methods

Fifty-five normotensive patients were studied. Forty of these had evidence of “sympatheticotonia” manifested by: (1) a marked fall in skin temperature following exposure to cold for 20 minutes, (2) cold, clammy extremities at ordinary room temperature, and (3) acrocyanosis or Raynaud’s phenomena. Fifteen patients had normal peripheral vascular systems. Twelve had had unilateral sympathectomies for “abnormal vasospasm” or causalgic states.

Thirty-six patients received 60 to 200 mg. of oral Dibenzyline in single or divided doses, eight were given 0.7 to 1.0 mg. per kilogram in a 200 cc. infusion over a 35 to 40 minute period, 10 were given 1 mg. per kilogram diluted in 10 cc. of saline solution intravenously within a four to seven minute period, and six received intra-arterial Dibenzyline (35 to 80 mg.) in the femoral artery within a three to four minute period. Some patients were given both oral and parenteral medication.

Observations were carried out in a constant temperature room with the patients lightly clothed.

Series of determinations were made in a warm environment, 25 to 27 C. (77 to 82 F.); at usual room temperatures, 22 to 25 C. (71.5 to 77 F.); at cool environments, 19 to 22 C. (66 to 71.5 F.); and in a cold room, 10 to 19 C. (50 to 66 F.).

Skin temperatures in all patients were determined with the Leeds Northrup Potentiometer. The venous occlusion plethysmograph\(^1\) was used to measure digital blood flow in 19 subjects. Blood pressure and blood flow responses following 1.0 mg. of intravenous Neosynephrine and immersion of the hand in water at 4 C. (39 F.) were determined before and after administration of Dibenzyline in 12 patients in order to judge the degree of sympathetic blockade.

### RESULTS

#### Time of Onset of Action

Following intravenous injection of 50 to 75 mg. of Dibenzyline over a four to seven minute period, the first evidence of effect was usually noted within 5 to 15 minutes. A significant adrenergic blockade, however, was not established for 30 to 40 minutes. Intra-arterial administration did not produce a more rapid effect. Onset of action following oral administration or an intravenous infusion given over a 30 to 45 minute period varied a great deal from person to person and even in the same individual after repeated doses. Duration of action following a single dose varied between 5 and 36 hours.

#### Establishment of an Adrenergic Blockade

Evidence of an adrenergic blockade (fig. 1) occurred in the following sequence:

1. Partial to complete inhibition of pupillary dilatation; pupils could not be dilated with Paredrine. Homatropine produced satisfactory dilatation.

2. Nasal congestion, indicating blockade of sympathetic vasoconstrictor fibers to the nasal blood vessels; local application of Neosynephrine did not relieve the congestion.

3. Definite diminution of sweating at average room temperature. Complete inhibition of sweating as determined by the use of the cobalt chloride “hot box” technic did not occur.

4. Postural hypotension and tachycardia. The fall in blood pressure in the upright position was only partially prevented by the use of ace bandages or tourniquets applied to the thighs. It was usually decreased considerably by the application of a tight abdominal binder. These findings were interpreted to indicate that at least part of the postural blood pressure changes were secondary to a release of splanchnic vascular tone in addition to some pooling of blood in the lower extremities. A significant fall in recumbent blood pressure did not occur.

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**Fig. 1. Outline of time of onset of effect and results of adrenergic blockade with Dibenzyline.**

* Not constant with above doses.
(4) A partial inhibition of the blood pressure rise after immersion of the hand in water at 4 C. (39 F.) for one minute in the 12 patients tested. Complete blockade was noted in only two. A partial or complete inhibition of the blood pressure rise following 1.0 mg. of intravenous Neosynephrine occurred in 10 patients. In two, a transient fall in pressure occurred after Dibenzyline (fig. 2). As recorded plethysmographically, the pulse volume decrease, usually noted after the above procedures, was completely eliminated in only two cases.

Effect on Skin Temperature and Blood Flow

The response obtained varied greatly. It depended upon the temperature of the room at the time Dibenzyline was administered, whether the upper or lower extremities were studied, and upon the degree of vasoconstriction present when the drug was given.

Results at Moderate Room Temperatures (22 to 25 C.). At ordinary room temperatures (22 to 25 C.) (71.5 to 77 F.) and at temperatures above 25 C., a rise in skin temperature of from 4 to 7 C. (7 to 12 F.) and/or blood flow (three to eight times control levels) uniformly occurred in the upper extremities. Sixty to 180 mg. orally or 1 mg. per kilogram intravenously produced a gradual increase in pulse volume, blood flow, and skin temperature which was greatest one and one-half hours after the administration of the drug. In four patients who had had unilateral dorsal sympathectomies for causalgic states or "vasospastic" phenomena, Dibenzyline produced changes in the normal contralateral extremity which compared favorably with those on the denervated side (fig. 3). In the doses administered, abnormal vasoconstriction was abolished.

Skin temperature determinations were not closely correlated with blood flow results at high skin temperatures; a rise from 31 to 32 C. (88 to 89.5 F.), although seemingly slight, actually represented a 50 to 100 per cent increase in blood flow in some cases. Skin temperature changes from 22 to 30 C. (71.5 to 86 F.) usually paralleled alterations in blood flow. There was a delay in skin temperature response as compared to blood flow response.

Oral or intravenous Dibenzyline produced an increase in skin temperature (4 to 8 C.) (7 to 14 F.) and/or blood flow (two to six times resting level) in the lower extremities at a room temperature of 22 to 25 C. in all but four patients. The changes in the intact limb equaled those produced by lumbar sympathectomy in 7 of the 10 patients who had had unilateral denervation prior to the study (figs. 4a and 4b). In the other three, increases were less than in the sympathectomized limb. In patients with a high degree of sympathetic overactivity, as evidenced by the presence of hyperhidrosis and cold and cyanotic extremities, marked vasodilatation was not obtained in the lower extremities with the doses used. In general, results obtained with intravenous Dibenzyline were more constant than with oral medication.
Thirty-five milligrams of intra-arterial Dibenzyline produced no appreciable change in skin temperature in the injected extremity.

Figure 4(a). Effect of intravenous Dibenzyline (1 mg. per kilogram) on blood flow pulse volume and skin temperature in a normal as compared with a denervated lower extremity. Skin temperature in the denervated limb does not reflect the decrease in blood flow or pulse volume that results from "redistribution" of blood.

(b). Pulse volume tracing before and after Dibenzyline (688A) in same patient as figure 4a. Slow speed used during control tracing. Pulse volume greater in intact limb after Dibenzyline than in denervated limb.

Fifty milligrams or more produced a rise in skin temperature from 5 to 9 C. in five of the six patients tested. In one patient with a unilateral sympathectomy, temperatures on the contralateral injected limb rose to equal those of the denervated limb. Evidence of marked sympathetic overactivity was present in the one patient who did not obtain a rise of more than 3 C. (5 F.). In only one instance was there evidence that the drug was "trapped" in the injected extremity. In the other patients, systemic effects occurred and there was no evidence to suggest a more marked effect on flow in the injected limb following intra-arterial injection.

Results at Cool Temperatures (19 to 22 C.). At room temperatures of 19 to 22 C., a rise in skin temperature (6 to 12 C.) (11 to 21.5 F.) and/or blood flow (three to eight fold increase) in the upper extremities occurred in only 14 of 20 patients who received oral Dibenzyline. A rise in skin temperature and blood flow was noted in six of eight patients who were given the drug intravenously. All of those who did not obtain a satisfactory response were patients who showed evidence of increased vasoconstrictor tone before therapy.

Results in the lower extremities were unpredictable. In four patients with normal extremities, an increase in skin temperature and blood flow occurred. Only one out of eight patients with increased "vasomotor tone" tested at this temperature experienced a significant effect upon blood flow. The other seven obtained poor responses from both oral and intravenous medication.

Changes in peripheral circulation did not occur despite the fact that other effects indicative of at least a partial adrenergic blockade were present, namely, stuffy nose, miosis, postural tachycardia, and blockade of the blood pressure response to cold stimuli.

Results of Cold Room Studies. Thirty-one patients were given 60 to 120 mg. of oral Dibenzyline while at a room temperature of 22 to 25 C. and after 90 minutes were placed in a cold room (12 to 15 C.) for 20 minutes. This procedure was carried out on numerous occasions over a period of five to six weeks in several cases. Six of these patients were considered to have normal extremities. Fourteen had had unilateral dorsal or lumbar sympathectomies and of these, six were considered
to have normal contralateral limbs. Eleven had definite evidence of sympathetic overactivity as manifested by increased sweating, acrocyanosis, Raynaud's phenomena, and an abnormal skin temperature response to a cold environment.

In the six patients with normal extremities, the skin temperature upon exposure to cold averaged 8 C. (14 F.) higher after Dibenzyline therapy than before. In those with unilateral sympathectomies, the degree of “protection”

![Fig. 5. Comparative effect of Dibenzyline and sympathectomy on skin temperature response to cold (lower extremity). Lower extremity skin temperature response to cold (20 minutes at 15.4 to 17 C.) in five patients before and after unilateral limb denervation by lumbar sympathectomy. Following Dibenzyline, “vasoconstrictor” response is blocked to a considerable degree in the intact normal extremity. Degree of “blockade,” however, is not as marked as on denervated side.]

against vasoconstriction following exposure to cold environment was considerable in the intact limb. It did not, however, equal the results obtained by sympathetic denervation. Five cases illustrating the effect of Dibenzyline as compared with sympathectomy are shown in figure 5.

The degree of “protection” was usually less in patients with evidence of excessive vasoconstrictor activity, but was significant (over 4 C.) in all but four cases. The effectiveness of Dibenzyline decreased somewhat following repeated studies. It was also noted that the temperature response to cold in the sympathectomized extremities partially returned within six to eight weeks following denervation. Only a slight increase of “vasomotor tone” was noted after that time, several patients having been studied as long as seven years after a sympathectomy.

Ten patients received oral Dibenzyline (100 to 100 mg.) while at a room temperature of 15 C. No effect upon skin temperature in either upper or lower extremities occurred despite the presence of miosis, stuffy nose, and postural tachycardia.

Toxicity and Side Effects

The major side effects encountered are listed in table 1. With the exception of palpitations and extreme drowsiness, the side effects were not severe in this group of patients without evidence of cardiac or pulmonary disease. (In a patient with primary pulmonary arteriosclerosis who was not included in this series, sudden death, following respiratory and cardiac arrest, occurred approximately eight minutes after he received 40 mg. of Dibenzyline intravenously over a five to seven minute period. The patient was taking quinidine and had received 0.6 Gm. one and one-half hours before Dibenzyline was given.) Following repeated doses of the drug, reactions were usually less marked, but in some patients no relief was noted. Symptoms often lasted as long as 48 to 72 hours after a single large dose.

Patients were usually kept in bed, either flat or semirecumbent, for two to three hours following intravenous administration of Dibenzyline and were cautioned regarding rapid postural changes for the next 24 to 48 hours. Those who received smaller oral blocking doses only occasionally experienced difficulty and usually remained ambulatory. No actual syncope occurred in normotensive patients although several experienced episodes of

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<tr>
<th>Table 1.—Toxicity and Side Effects of Dibenzyline (SKF 688A) in Normotensive Patients</th>
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<tr>
<td>1. Dryness of mouth and stuffy nose .................................. 49 pts.</td>
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<tr>
<td>2. Transient dizziness, weakness, fatigue .......................... 27 pts.</td>
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<tr>
<td>3. Transient dizziness and palpitations .............................. 20 pts.</td>
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<tr>
<td>4. Decrease in amount of seminal fluid ............................... 14 pts.</td>
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<tr>
<td>5. Nausea and vomiting ................................................. 3 pts.</td>
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<tr>
<td>6. Transient restlessness and tenseness ................................ 1 pt.</td>
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<td>Total number of patients studied ...................................... 55</td>
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“faintness” (an “all gone” feeling) and had to lie down to avoid fainting.

**DISCUSSION**

We have been able to confirm the observations that Dibenzyline is a moderately potent adrenergic blocking agent, effective parenterally or orally. The drug should be given slowly, preferably in an infusion over a 30 to 45 minute period when used intravenously. It does not appear to be as toxic as the parent substance, Dibenamine. Its administration, however, in patients with cardiac or pulmonary disease, or patients receiving other potent drugs such as Quinidine should be carried out with great caution. If the drug is used for these patients the oral route is to be preferred. Intravenous injection, although effective, does not appear to produce a “local” effect without systemic manifestations of action and consequently presents no advantages over other methods of administration.

Onset of action following intravenous or intra-arterial injection varies, but a satisfactory blockade is usually produced in approximately 30 to 60 minutes after the injection. In an occasional case, a good blockade is present within 10 to 20 minutes. This is in contrast to the action of other blocking agents—the methonium derivatives and Priscoline—where parenteral administration produces an almost immediate response. Orally, adrenergic blockade is not established for 60 to 90 minutes. It has been suggested that an “equilibrium” phase between Dibenamine-like substances and a “receptor” substance exists before the actual chemical blockade occurs. This would serve to explain the delay in onset of action of Dibenzyline. The duration of action following a large blocking dose varies between 3 and 30 hours. Whether the drug is stored in fat depots and slowly released or remains in a firm chemical bond with a “receptor” substance has not been determined.

The absorption of Dibenzyline orally seems to be complete in some patients. These achieve a satisfactory blockade on 1 mg. per kilogram regardless of the route of administration; others require 2 to 2.5 mg. per kilogram orally to produce an equivalent effect. In an occasional patient, evidence of drug action is not observed. These factors of absorption may account for the varying results reported when the oral route of administration is used.

In the doses employed, Dibenzyline appears to produce a blockade of successive vascular beds. Apparently the areas with the least amount of “sympathetic tone” are affected first. In most instances nasal vasconstriction and pupillary dilatation are inhibited before other effects are noted. Indirect evidence of a release of splanchnic vascular tone (postural hypotension relieved by an abdominal binder) occurs at approximately the same time as the blockade of the blood pressure response to cold stimuli or neosynephrine. In contrast to the above effects, the drug does not uniformly inhibit the sympathetic nervous system effect on peripheral blood vessels as evidenced by skin temperature and blood flow response. Increase in skin temperature and/or blood flow does not uniformly occur in the lower extremities, especially in patients with an abnormally high degree of vasoconstrictor tone despite the demonstration of an adrenergic blockade in other areas. Upper extremity responses are more constant. This difference in upper and lower extremity response is also seen when other peripheral blocking agents such as C.C.K.179 (Hydergine)* or Priscoline are tested. Other observers have noted this difference in response. When ganglionic blocking agents, pentamethonium† or hexamethonium‡ or tetraethylammonium chloride are given, however, the most uniform response is noted in the lower extremities. Other observers have suggested that the site of blockade is the determining factor in these varying responses. It is also possible that the peripheral blocking agents in the doses given do not produce a blockade complete enough to overcome the vasoconstrictor tone of the lower extremities. This explanation appears more probable in view of the lack of blood flow response in the patients who received Dibenzyline at room temperatures below 21 C.

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* Supplied by Sandoz Pharmaceutical Co., New York, N.Y.
† Supplied by Parke Davis Co., Detroit, Mich.
‡ Supplied by E. R. Squibb, Co., New York, N.Y.
EFFECTS OF DIBENZYLINE

(72 F.), as contrasted to the satisfactory response at room temperatures of 22 to 25 C. At the lower room temperatures a fixed degree of vasoconstrictor tone, which apparently cannot be overcome, is maintained.

When Dibenzyline is given, however, while at moderate room temperatures (22 to 25 C.) and the patient then subjected to a cool or cold environment, a marked vasoconstrictor response is prevented in both the upper and lower extremities. This observation is of great importance in considering the clinical usefulness of the drug. Since the agent is usually administered to patients at ordinary room temperatures, an effect on peripheral blood flow and skin temperature may be expected and a blockade of the pressor and vasoconstrictor response to subsequent cold environments will be obtained.

Its oral effectiveness and long duration of action are also important factors which indicate that Dibenzyline may have a place in the treatment of peripheral vascular disease. The drug, however, especially when given orally, does not appear to be suitable for use in increasing blood flow to an extremity in patients who receive it while in a cool or cold environment. In this regard it is not as effective, at least in the dosages given, as Hexamethonium or surgical nerve blocks which produce more constant results in cool environments.17

The degree of “protection” produced by Dibenzyline against cold is not as great as that provided by surgical sympathectomy, but it appears to be sufficient to produce clinical results. A gradual return of the vasoconstrictor ability of the peripheral vessels has been noted during the weeks or months following sympathectomy.18, 19 This was observed in our patients who were studied after sympathectomy and following repeated doses of Dibenzyline. Evidence of sympathetic denervation or blockade was present in other areas, however, and it was concluded that a vascular adjustment or an increase in “intrinsic vascular tone” had occurred. This may explain the occurrence of so-called “tolerance” to drug effect which occurs on prolonged Dibenzyline therapy. In only a few patients could actual tolerance be demonstrated. In many instances the decreasing effect may represent an “adjustment” similar to that following surgical denervation.

The side effects of this drug are related to its sympathetic blocking action and are occasionally troublesome. The soporific effect of Dibenzyline suggests some central action, perhaps on the hypothalamic or cortical areas.

The “quinidine-like” effect of the drug on heart muscle14 was not noted in the group of normal patients but should be kept in mind when Dibenzyline is given to patients with cardiac disease.

Summary

1. Dibenzyline appears to be a moderately potent, specific adrenergic blocking agent, effective parenterally (1 mg. per kilogram) and orally (1 to 25 mg. per kilogram). Duration of action is from 3 to 72 hours.

2. Blood flow responses to Dibenzyline are irregular when the drug is given in a cool or cold room, especially if the patient has evidence of increased vasoconstrictor tone.

3. When Dibenzyline is given at room temperatures, an increase in blood flow and skin temperature, and at least a partial blockade of vasomotor responses to cold and intravenous neosynephrine is noted in both upper and lower extremities. The degree of response is not always comparable to results obtained with sympathectomy, especially in the lower extremities, but appears to be adequate for clinical effect.

4. These observations suggest that the drug may be of value in certain cases of peripheral vascular disease, acrocyanosis, and hypertension where a sympathetic blockade is indicated. Its oral effectiveness and long duration of action present definite advantages over other available blocking agents. It should be given at room temperatures to obtain maximum effect. Side effects and “adjustment” or “tolerance” to drug effect may limit its use in clinical medicine.

Sumario Español

La Dibencilina es un agente bloqueador adrenérgico oralmente efectivo, moderadamente potente y de acción prolongada. La droga es
capaz de por lo menos parcialmente evitar la repuesta vasoconstrictora al frío y a la neosinafrina inyectada. Los resultados en cuanto a circulación de sangre y la repuesta a la temperatura a esta droga no siempre igualan a los resultados de una simpatectomía quirúrgica, pero el grado del efecto aparece ser suficiente para producir repuestas clínicas. Efectos no deseadables y el desarrollo de "tolerancia" puede que limiten el uso de la Dibencilina en la medicina clínica.

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Effect of Dibenzyline on Skin Temperature, Peripheral Blood Flow, and Vasomotor Responses in Normal Patients and Patients with Increased Vasoconstrictor Tone
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