The Action of SKF 688A (Phenoxyethyl Derivative of Dibenamine) upon Certain Functions of the Sympathetic Nervous System in Man

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A Dibenamine analogue was administered orally to five hypertensive and 10 normotensive subjects over periods from 14 to 21 days. Its adrenergic blocking effect was studied by observing blood pressure, pulse rate, skin temperature of the toes and the pupillary mechanism. Nasal congestion, weakness, listlessness, dizziness, drowsiness and palpitation were persistent sequelae of adrenergic blocking. The drug was found valuable for investigation of autonomous nervous system functions and may hold promise as a therapeutic agent for the treatment of arterial insufficiency and some types of hypertensive subjects.

SKF 688A (N-phenoxyisopropyl-N-benzyl-B-chlorehylamine hydrochloride) is a new adrenergic blocking agent. It is structurally and pharmacologically similar to Dibenamine but in contradistinction to Dibenamine, is tolerated orally. In animals, SKF 688A has been shown to be 10 times as potent as Dibenamine intravenously and twice as active by mouth.1

The pharmacologic actions of Dibenamine have been described by Nickerson, Goodman, Nomaguchi2 and others.3-6 Following intravenous injection of Dibenamine in man, a decrease in systolic and diastolic blood pressure was noted in some, and orthostatic hypotension and marked pupillary contraction were noted in all patients.1 All authors were able to demonstrate increased peripheral blood flow in patients with peripheral vascular disease. Although Haimovici4 reported orthostatic hypotension in all patients tested, significant change in the resting blood pressure occurred only when hypertension was present. A marked reduction in both systolic and diastolic blood pressure was produced in patients with “benign” hypertension, but only a slight decrease occurred in those with “malignant” hypertension. Myers and co-workers6 noted temporary symptomatic remission in 7 of 10 patients with hypertensive encephalopathy. More recently, intravenous injection of Dibenamine has been used to reduce intraocular pressure in glaucoma when other medical agents were ineffective.7, 8 In general, its use has been limited by the severe systemic manifestations and the necessity for intravenous administration.

Preliminary studies with 688A in human subjects9 have shown that postural hypotension, miosis, and vasodilatation follow the use of this drug by mouth as well as intravenously. Other effects reported were faintness, weakness, fatigue, diarrhea, drowsiness, headache, nasal congestion and blurred vision.

Moser and co-workers10 administered 688A to 19 patients. Most cases developed postural tachycardia, miosis and nasal congestion. Extreme postural hypotension developed in one case. The blood pressure fell to normal or slightly above in six of nine hypertensive patients under the age of 50. The fall in blood pressure was maintained as long as the drug was continued, but rose within 36 to 72 hours after the drug had been stopped.
METHODS AND MATERIAL

The plan of the present study was to follow the effects of the drug over a prolonged period of administration (just as the drug would be given clinically) rather than to measure the vasodilator effects for only a few hours following a single dose. From patients during a control period and while the drug was being administered. Temperatures were recorded every 27 seconds for 180 minutes on a Leeds and Northrup speedomax in a constant temperature room at 19.5 ± 1°C and 50 ± 5 per cent humidity. All observations were made following abstinence from food and tobacco for at least four hours at approximately the same time of day with one exception (JW). Likewise an interval of about five hours after the last dose of the drug preceded each period of observation.

An ophthalmologic survey was carried out on each patient. Intraocular tensions, pupillary responses, measurements of accomodation, and visual acuity determinations were recorded throughout the three periods of the experiment.

All tensions were measured with the same Schiotz tonometer, with the patient at the same reclining

**Table 1.—Summary of Clinical Data of Patients Studied and Comparison of Their Resting Blood Pressures before and during Administration of SKF-688A**

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>BUN</th>
<th>EKG</th>
<th>Control BP</th>
<th>BP under 688A*</th>
<th>Days on 688A†</th>
</tr>
</thead>
<tbody>
<tr>
<td>JK</td>
<td>64</td>
<td>M</td>
<td>Hypothyroid, cataracts, generalized arteriosclerosis</td>
<td>18.5</td>
<td>Normal</td>
<td>150/58</td>
<td>150/60</td>
<td>14</td>
</tr>
<tr>
<td>MR</td>
<td>73</td>
<td>M</td>
<td>Diabetes mellitus, cataracts, arteriosclerosis obliterans</td>
<td>20.8</td>
<td>Myocardial damage</td>
<td>132/94</td>
<td>130/80</td>
<td>19</td>
</tr>
<tr>
<td>VR</td>
<td>62</td>
<td>M</td>
<td>Arteriosclerotic heart disease; arteriosclerosis obliterans</td>
<td>20.8</td>
<td>Atypical RBBB</td>
<td>150/90</td>
<td>125/65</td>
<td>17 and 18†</td>
</tr>
<tr>
<td>RA</td>
<td>50</td>
<td>M</td>
<td>Portal cirrhosis, hypertension, arteriosclerosis obliterans</td>
<td>10.1</td>
<td>Left axis deviation</td>
<td>160/90</td>
<td>160/80</td>
<td>9</td>
</tr>
<tr>
<td>DF</td>
<td>46</td>
<td>M</td>
<td>Hypertensive cardiovascular disease</td>
<td>38.6</td>
<td>Left axis deviation</td>
<td>230/140</td>
<td>170/130</td>
<td>3</td>
</tr>
<tr>
<td>RS</td>
<td>60</td>
<td>M</td>
<td>Hypertension, right hemiplegia</td>
<td>18.2</td>
<td>Left axis deviation</td>
<td>220/130</td>
<td>190/120</td>
<td>12</td>
</tr>
<tr>
<td>WB</td>
<td>29</td>
<td>M</td>
<td>Hypertension, subacute nephritis</td>
<td>21.5</td>
<td>Normal</td>
<td>145/105</td>
<td>130/90</td>
<td>16</td>
</tr>
<tr>
<td>JC</td>
<td>46</td>
<td>M</td>
<td>Arteriosclerotic heart disease, nephrosclerosis</td>
<td>68.0</td>
<td>Auricular fibrillation, LBBB</td>
<td>160/80</td>
<td>160/80</td>
<td>5</td>
</tr>
<tr>
<td>AG</td>
<td>40</td>
<td>F</td>
<td>Polynephritis</td>
<td>10.5</td>
<td>Normal</td>
<td>110/70</td>
<td>116/74</td>
<td>16</td>
</tr>
<tr>
<td>CH</td>
<td>13</td>
<td>M</td>
<td>Rheumatic fever</td>
<td>15.5</td>
<td>Normal</td>
<td>110/80</td>
<td>110/80</td>
<td>16</td>
</tr>
<tr>
<td>JR</td>
<td>60</td>
<td>M</td>
<td>Arteriosclerotic heart disease, duod. ulcer, left hemiplegia</td>
<td>10.6</td>
<td>Right bundle branch block</td>
<td>160/80</td>
<td>155/80</td>
<td>16</td>
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<tr>
<td>FA</td>
<td>66</td>
<td>M</td>
<td>Pulmonary fibrosis, bronchiectasis</td>
<td>12.5</td>
<td>Left axis deviation</td>
<td>110/60</td>
<td>80/56</td>
<td>1</td>
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<tr>
<td>JF</td>
<td>52</td>
<td>F</td>
<td>Portal cirrhosis</td>
<td>13.0</td>
<td>Normal</td>
<td>124/80</td>
<td>130/80</td>
<td>15</td>
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<tr>
<td>YL</td>
<td>48</td>
<td>F</td>
<td>Hypertension, malignant</td>
<td>19.5</td>
<td>Left axis deviation</td>
<td>260/150</td>
<td>230/130</td>
<td>11</td>
</tr>
<tr>
<td>JW</td>
<td>41</td>
<td>M</td>
<td>Hypertensive cardiovascular disease</td>
<td>20.0</td>
<td>Sinus tachycardia, myocardial involvement</td>
<td>175/98</td>
<td>130/80</td>
<td>7</td>
</tr>
</tbody>
</table>

* The readings listed under 688A are the lowest recorded during the experimental period.
† Dosage of SKF-688A was 120 mg. per day.
‡ This patient received 688A for two periods, one for 17 days and the second, for 15 days.

this type of study it would also become clear whether repeated doses continued to elicit the original response.

Fifteen patients were studied before, during, and after administration of 688A in doses of 40 mg. every eight hours (table 1). Twelve-lead electrocardiograms were taken on 12 of them before and during administration of the drug. Blood pressure and pulse rate were recorded daily in both the sitting and standing positions on all patients.

Skin temperatures were recorded in 10 of the
angle, and at the same hour each day. Pupillary measurements were recorded under standard lighting conditions. Tearing was evaluated by means of the Schirmer test, and the Hertel Exophthalmometer was used to ascertain any change in position of the

RESULTS

The effects obtained by oral administration of SKF 688A were, in general, like those obtained with intravenous Dibenamine. One pa-

![Image of tables and graphs]

Fig. 1. Four examples of the response of blood pressure and pulse rate to administration of SKF 688A are shown. A. Marked response in both pulse rate and blood pressure. B. Relatively little response of either. C. Lack of response in blood pressure with moderate rise in pulse rate. D. Little response in blood pressure with a curious rise in rate at the end of administration of the drug.

globe. Tests for accommodation were performed (utilizing the Duane Card) following adequate correction of refractive error. In addition, concurrent changes in the refractive state were sought. Ten per cent Neosynephrine (Winthrop-Stearns) was the drug used topically to mimic sympathetic stimulation of the iris. Reactions to local instillation of 4 per cent cocaine hydrochloride, 1 per cent Paredrine hydrobromide (SKF), 5 per cent homatropine hydrobromide, 0.25 per cent eserine salicylate, and 2 per cent pilocarpine hydrochloride were also studied.

tient (VR) was treated with 688A twice, with an eight-week interval between. In five patients the drug was stopped after periods of administration ranging from 1 to 11 days because of various “toxic” reactions. Ten patients were maintained on it for periods of 14 to 21 days.

Circulatory Effects

The resting blood pressure was significantly reduced in seven patients and was unchanged
in eight (table 1). Postural hypotension was produced in eight patients. Four did not have any changes in blood pressure on standing, and in three, observations could not be made in the erect position.

In seven patients there was an increase in pulse rate during the drug period. This tachycardia was marked in five. It was still more marked in the erect position. Even on rest it persisted for about a week after the drug was stopped. In one patient (YL) tachycardia began just at the end of the period of administration of the drug. The tachycardia was generally more marked on standing. Figure 1 illustrates the different types of response of blood pressure and pulse rate.

The development of auricular fibrillation was noted in JW after seven days on 688A. When the drug was stopped, the electrocardiogram showed auricular flutter with 2:1 block which had become a 4:1 block two days later and then sinus tachycardia. The day previous to the development of the auricular fibrillation he had received 4 cc. of Mercuhydrin and 1 Gm. of aminophylline intravenously with the loss of 12 pounds. Subsequent to later intravenous injections of aminophylline, transient episodes of auricular fibrillation occurred. The role, if any, which SKF 688A played in producing this arrhythmia, is very dubious.

The temperature of the toes was significantly higher in all patients while taking the drug (table 2 and fig. 2). In two patients (MR and VR) the elevation of temperature of the toes persisted for 17 and 13 days, respec-

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Great Toes (Average)</th>
<th>Middle Fingers (Average)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>688A</td>
</tr>
<tr>
<td>JK</td>
<td>21.6</td>
<td>29.8</td>
</tr>
<tr>
<td>MR</td>
<td>24.1</td>
<td>26.7</td>
</tr>
<tr>
<td>VR</td>
<td>23.9</td>
<td>21.5</td>
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<tr>
<td>WB</td>
<td>19.1</td>
<td>20.1</td>
</tr>
<tr>
<td>JC</td>
<td>20.7</td>
<td>29.2</td>
</tr>
<tr>
<td>AG</td>
<td>19.2</td>
<td>20.9</td>
</tr>
<tr>
<td>CH</td>
<td>22.4</td>
<td>26.1</td>
</tr>
<tr>
<td>JF</td>
<td>19.5</td>
<td>29.0</td>
</tr>
<tr>
<td>YC</td>
<td>21.2</td>
<td>26.0</td>
</tr>
<tr>
<td>JW</td>
<td>31.0</td>
<td>33.8</td>
</tr>
</tbody>
</table>

The temperatures given are the temperatures at the end of a 180 minute period of adaptation in the constant temperature room at 21°C., 50 per cent humidity. Since the differences between the temperature of the correspondent digits of the two sides were small, the average of the two is given.

* A rise is indicated, unless the sign is minus.

Fig. 2. Skin temperature response to SKF 688A in both great toes of 10 subjects. The solid lines connect mean values.

Fig. 2. Skin temperature response to SKF 688A in both great toes of 10 subjects. The solid lines connect mean values.

An inability of the iris to dilate in darkness developed as early as 24 hours after SKF 688A had been started and was present in all cases after 96 hours. The diameter of the pupils was the same in a normally lighted room after medication as before (2.5 to 3 mm.). The pupil
did, nevertheless, continue to respond to a very bright light, to convergence and to eserine and pilocarpine by further contraction. The pupils also lost their ability to dilate with 10 per cent Neosynephrine and this loss persisted for a variable period of time (from less than 24 hours to nearly a week) after withdrawal of the drug. Likewise, instillation of 4 per cent homatropine hydrobromide did, however, cause some pupillary dilation.

After SKF 688A had been discontinued, normal response to darkness and Neosynephrine returned in some instances within 24 hours and all individuals responded fully after seven days. There was no direct correlation between total dosage of SKF 688A and the rapidity of recovery of the ability of the iris to dilate after stopping the drug.

Significant changes were not noted in intraocular tension, appearance of fundi, Schirmer tests, accommodative findings, refractive errors, position of the globes, palpebral fissure measurements, and extraocular muscle functions.

Effects on Other Organs

All patients noted nasal congestion within 48 hours, and in two, this was accompanied by epistaxis. Weakness and listlessness occurred in five patients. Four complained of headaches and three developed vomiting, with diarrhea in one. Three complained of dizziness, which was especially marked in one. Three patients noted palpitation and three were noted to be excessively drowsy. A short resume of one case is presented since the development of the pneumonia may be considered to have been due to congestion of the mucous membranes of the respiratory tract even though the total dose was exceedingly small.

One patient, a 65 year old white man with bronchietasis, pulmonary fibrosis and emphysema, was given 120 mg. of 688A on the twenty-third day of hospital observation. During that day it was noted that his temperature was slightly elevated. The following day he became dyspneic and drowsy, but could be easily aroused. His blood pressure was 80/56 as compared to his normal of 110/60. His temperature was 100 F. and pulse was 120. The breath sounds were diminished over the right lung and there was bronchial breathing at the left base. X-ray films showed an infiltration in the left mid and lower lung field and in the right lower lung adjacent to the heart. An electrocardiogram showed a sinus tachycardia with some decrease in amplitude of the T waves. The 688A was stopped after a total dose of only 120 mg. and he was given an infusion of 1000 cc. of normal saline. His blood pressure rose to 96/60 following the infusion and remained at normal levels for the next two days. He was treated with antibiotics and appeared improved despite the fact that his pneumonia spread to the right lung base. Four days later he expired with a massive pulmonary hemorrhage.

Discussion

In doses of 120 mg. daily by mouth, 688A is a powerful adrenergic blocking agent. In fact, a smaller dose may be effective in many subjects and cause fewer side effects. The effects were evident within 24 hours; nasal congestion appeared to be the first clinical sign of adrenergic blocking. The drug is long acting and effects
on the peripheral circulation were observed as long as 13 and 17 days and on pupillary response, as long as seven days after the drug had been stopped. Prolonged action had also been noted with Dibenamine. Brodie and associates have suggested that prompt localization of the drug in body fat with subsequent slow release may be responsible for this phenomenon. Clinically, one would expect that obese people would have the most prolonged response to the drug. The range of obesity was not sufficiently great in our group of patients to examine this point.

Correlation between response in blood pressure and in pulse rate was not demonstrable. Correlation between drop in blood pressure and rise in skin temperature of the toes was likewise unclear but tended to be negative. Of 10 subjects, seven had a toe temperature increase of 3 degrees or more. Only one of these experienced a drop in blood pressure, while two of the three who had an increase of less than 3 degrees had a drop in blood pressure. The explanation for the tachycardia after adrenergic blockade is not clear; it has been noted with other similar-acting drugs.

Electrocardiographic changes secondary to 688A were minimal and in general explained by increase in rate.

The responses of the fingertips were variable and confirm the fact that the fingers are unsatisfactory indicators of vasodilator effect. Of a total of five subjects with obliterating arteriosclerosis, two reported here and three tested previously, only one had drop in blood pressure, while all of them had increase in temperature of the toes.

All response of the dilator muscle of the iris to sympathetic innervation was lost under the influence of SKF 688A. The position taken by the iris is due to the tonus of the sphincter muscle, and the fact that miosis did not occur leads to the conclusion that very little sympathetic stimulation of the part is present under static conditions. That the sphincter is not in spasm is demonstrated by the size of the pupil, its reaction to light, as well as to pilocarpine and eserine. It is further confirmed by the fact that when the sphincter tonus is removed by the use of homatropine (which blocks parasympathetic response) the pupil assumes an intermediary size.

The fact that 688A had no influence on normal intraocular tension does not preclude its trial under abnormal conditions of ocular pressure. The interplay between sympathetic and parasympathetic control has been lately under serious consideration as a possible etiologic factor in glaucoma.

Four patients complained of slight blurring of distant vision coincident with objective pupillary response to the drug. On examination there was no objective diminution to visual acuity nor was there a demonstrable change in accommodation. As a matter of fact, visual acuity was actually increased; the patients were able to see a blurred line on the chart where they had seen none at all before administration of the drug. This is obviously due to the maintenance of a small pupil in a dark room.

Nasal congestion, weakness and listlessness, dizziness, drowsiness and palpitation which were observed are more or less to be expected as direct physiologic sequelae of adrenergic blocking. It is interesting that all these effects had a great tendency to appear delayed and to outlast considerably the period of drug administration. In contrast to this, nausea and vomiting tended to disappear after the first two or three days, while administration of the drug was continued.

SKF 688A will undoubtedly be of value in physiologic studies concerning the function of the autonomous nervous system. It may turn out to be of therapeutic value in glaucoma, in occlusive arterial disease of the extremities, and possibly in some types of hypertension. The drug is probably contraindicated in patients with chronic pulmonary disease, because of the congestion of the mucous membranes of the respiratory passages including those of the bronchial tree.

**Summary**

1. A new adrenergic blocking agent, SKF 688A (N-phenoxisopropyl-N-benzyl-B-chlorethylamine hydrochloride), was given to 15 patients in oral doses of 40 mg. every eight hours for periods from 14 to 21 days. Five of the patients were hypertensives.
2. The resting blood pressure was lowered in seven patients. Four of these had hypertension.

3. Five patients showed marked increase in pulse rate, which outlasted the administration of the drug by about a week; two had slight increase in pulse rate during the drug period; one had marked increase in pulse rate, starting at the end of the drug period; seven had no significant increase in pulse rate.

4. All patients showed significant rises in skin temperature of both big toes under action of the drug.

5. Impairment of pupillary dilator mechanism was observed in all patients within 72 hours after beginning of administration of the drug. The type of impairment is described in detail.

6. Nasal congestion, weakness and listlessness, dizziness, drowsiness, palpitation are sequelae of adrenergic blocking and are persistent. Nausea and vomiting tend to disappear after the first two or three days and are probably not due to the adrenergic blocking action.

7. Adrenergic blocking agents may aggravate the symptoms of patients with pathology of the respiratory tract.

8. SKF 688A is a valuable drug for investigation of autonomous nervous system functions and deserves thorough study as a therapeutic agent for the treatment of arterial insufficiency and some types of hypertensive subjects.

REFERENCES


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