Effects of Regitine (C-7337) in Patients, Particularly Those with Peripheral Arterial Vascular Disease

By Harold D. Green, M.D. and William T. Grimsley

This is a study of the clinical effects of Regitine, a new antiadrenergic drug, the pharmacologic properties of which are similar to those of Priscoline. Thirty-four patients, whose diagnoses fall into the peripheral vascular disease group and into a miscellaneous group were first given the drug intravenously and the responses were studied with skin temperature recordings in an attempt to predict the response to therapeutic administration of Regitine. The drug was then given orally for varying periods of time, with subjective and objective evidences of response, as well as side effects being noted. The results of these observations are set forth in the paper.

REGITINE, 2-[N-p'-tolyl-N-(m'-hydroxyphenyl) -aminomethyl]-imidazoline HCl, (C-7337), is an antiadrenergic drug first developed by Marxer and Miescher in 1947. Its pharmacologic properties were reported by Meier and Yonkman as being adrenergolytic in small doses and sympatholytic in higher concentrations, the latter being reported as greater than that of Priscoline, a progenitor in the imidazoline series. These antiadrenergic properties were tested in man by Hecht, Crandall and Samuels who obtained similar results and added the assumption of local vasodilatation. Studies using direct measurement of blood flow in the femoral artery of the dog demonstrated an increase in blood flow with injections of Regitine, per se, and showed that Regitine is capable of converting the vasoconstricting effect of epinephrine into a vasodilating effect in a dosage of 0.1 to 0.15 mg. per kilogram. Studies on normal students show that Regitine has an efficacy similar to Priscoline in relieving vasospasm induced by cold. It was felt, therefore, that clinical trial of the drug was justified and this report deals with the results of that trial conducted over an 18 months' period. The maximum duration of therapy for any one patient was 14 months, though many are continuing therapy. Most of the patients were given skin temperature studies, testing the drug intravenously, just as were the students. In the clinical evaluation of the drug, it was administered orally and a comparison made between the actual therapeutic response and the initial response to the intravenous injection.

MATERIAL AND METHODS

Thirty-four patients were studied. They may be divided into four groups, from the point of view of diagnosis, as in table 1, in order to evaluate the results of Regitine therapy in those particular disease states. Group I is comprised of 10 patients with the diagnosis of Raynaud's disease consisting of five females and five males varying in age from 20 to 60 years. Diagnosis of Raynaud's phenomena was considered when several of the following were present: upper or lower extremity involvement, ulceration, when present, limited to tips of digits, secondary sclerodermatous changes, prominent symptoms of coldness, pallor and aching aggravated by cold, changes in nail growth, peripheral pulsations palpable, and on skin temperature study under adequate ganglionic blocking drug shows practically normal maximum temperatures as contrasted to the occlusive diseases. The diagnosis of primary Raynaud's disease was made when the cause was unknown. Two patients were classified as secondary Raynaud's disease in view of possible nerve trunk irritation. In one the symptoms followed myocardial infarction with subsequent shoulder-hand syndrome. In the other the symptoms followed electrical burns to the hands.

Group II is composed of 14 patients with the diagnosis of arteriosclerotic peripheral vascular disease and is made up of 13 males and one female
### Table 1.

**Group I-A—Primary Raynaud’s**

<table>
<thead>
<tr>
<th>Case Age Sex</th>
<th>Temperature Studies*</th>
<th>Dosage and Duration</th>
<th>Simultaneous Therapy</th>
<th>Subjective and Objective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP Male 34yrs.</td>
<td>R2F</td>
<td>10.0°</td>
<td>60 mg. t.i.d. for 14 days</td>
<td>Thyroid Ext, 32 mg. Sym- pathectomy prior to Rx</td>
</tr>
<tr>
<td>113539 51yrs.</td>
<td>R2F</td>
<td>6.5°</td>
<td>30-60 mg. t.i.d. for 70 days</td>
<td>Vitamin B6 twice weekly</td>
</tr>
<tr>
<td>RLP Male 113539 51yrs.</td>
<td>R2F</td>
<td>10.5°</td>
<td>60 mg. q.i.d. for 14 mos.</td>
<td>None</td>
</tr>
<tr>
<td>LNJ 120757 41 yrs.</td>
<td>L2F</td>
<td>7.0°</td>
<td>60 mg. t.i.d. for 30 days</td>
<td>Thyroid Ext. 60 mg. Vitamin B6 I.M. 3x/w</td>
</tr>
<tr>
<td>SHW 124004 34 yrs.</td>
<td>R2F</td>
<td>8.5°</td>
<td>30-60 mg. t.i.d. for 25 days</td>
<td>Thiamine 50 mg. t.i.d.</td>
</tr>
<tr>
<td>LBM 130193 51 yrs.</td>
<td>R2F</td>
<td>7.0°</td>
<td>60-120 mg. 3-tis/d for 2 mos.</td>
<td>Thiamine 50 mg. t.i.d.</td>
</tr>
<tr>
<td>MFP 130078 33 yrs.</td>
<td>R2F</td>
<td>10.5°</td>
<td>30 mg. 3-tis/d for 1 mo.</td>
<td>Thiamine 50 mg. t.i.d.</td>
</tr>
<tr>
<td>Female L2F</td>
<td>11.5°</td>
<td>12.5°</td>
<td>90 mg. 3-tis/d for 1 mo.</td>
<td>Vit. B and C</td>
</tr>
<tr>
<td>RSH 114605 28 yrs.</td>
<td>L2F</td>
<td>11.5°</td>
<td>30-120 mg. t.i.d. for 1 mo.</td>
<td>Thiamine 50 mg. t.i.d.</td>
</tr>
<tr>
<td>Female R2F</td>
<td>9.5°</td>
<td>0 °</td>
<td>60 mg. 3-tis/d for 1 mo.</td>
<td>Vit. B and C</td>
</tr>
<tr>
<td>ECD 117546 54 yrs.</td>
<td>L2F</td>
<td>12.0°</td>
<td>30-60 mg. t.i.d. for 9 mos.</td>
<td>Low cholesterol diet, Thiamine 50 mg. b.i.d.</td>
</tr>
<tr>
<td>Male L2F</td>
<td>10.5°</td>
<td>2.0°</td>
<td>Low cholesterol diet, Thiamine 50 mg. b.i.d.</td>
<td>Marked subjective improvement at first, then gradual return of symp- toms.</td>
</tr>
<tr>
<td>Group I-B—Secondary Raynaud’s Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KWL 99875 26 yrs.</td>
<td>R2F</td>
<td>12.0°</td>
<td>120 mg. q.i.d. for 2 weeks.</td>
<td>Thiamine 50 mg. b.i.d.</td>
</tr>
<tr>
<td>Male L2F</td>
<td>11.5°</td>
<td>13.5°</td>
<td>30-120 mg. t.i.d., during very cold weather</td>
<td>Thiamine 50 mg. b.i.d.</td>
</tr>
<tr>
<td>FIF 122219 60 yrs.</td>
<td>R2F</td>
<td>10.5°</td>
<td>30 mg. t.i.d. for 3 mos.</td>
<td>None</td>
</tr>
<tr>
<td>Male L2F</td>
<td>14.0°</td>
<td>13.0°</td>
<td>60 mg. t.i.d. for 50 days</td>
<td>Vit. B with C, Thyroid Ext. 32 mg./d sympathectomy.</td>
</tr>
<tr>
<td>PFK 114578 46 yrs.</td>
<td>R2F</td>
<td>9.5°</td>
<td>Combination of Regitine (60 mg.) and Priscoline (25 mg.) t.i.d., 30 days</td>
<td></td>
</tr>
<tr>
<td>Male R2F</td>
<td>10.5°</td>
<td>10.0°</td>
<td>60 mg. t.i.d. for 50 days</td>
<td>Vit. B with C, Thyroid Ext. 32 mg./d sympathectomy.</td>
</tr>
</tbody>
</table>

* Temperature studies in response to either Etamon, 15 mg./Kg. or to Regitine, 0.5 mg./Kg., intravenously, prior to starting oral therapy.

The italicized figures are the responses of the affected extremities; the nonitalicized figures are the responses of the unaffected opposite normal extremity. The responses are expressed as the maximum temperature reached in the extremity in response to the drug administration, expressed in degree centigrade above the room temperature of 20°C.

Digit abbreviations: R—right; L—left; F—finger; T—toe; numeral indicates digit position.

The following patients had blood cholesterol values greater than 200 mg. per 100 ml.: group IB, FIF; group IIA, PEK, JPT, RVA, HMc, HGP, CDF, TLP, JGN, EAH; group III, WDM, HJW; group III, ANT; group IV, CHM.
TABLE 1—Continued

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Temperature</th>
<th>Studies</th>
<th>Dosage and Duration</th>
<th>Simultaneous Therapy</th>
<th>Subjective and Objective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHO</td>
<td>64820</td>
<td>Male</td>
<td>LIT 1.5°</td>
<td>Etamon I.V. 7°</td>
<td>30 mg. t.i.d., 5 days</td>
<td>Phlebotomy for polycytheemia</td>
<td>“Feet and legs haven’t hurt for 3 months.” No recurrent leg pain.</td>
</tr>
<tr>
<td>JPT</td>
<td>51yrs.</td>
<td>Male</td>
<td>RIT 0.5°</td>
<td>Regitine I.V. 2.5°</td>
<td>60 mg. t.i.d., 9 mos.</td>
<td>Right and left lumbar sympathectomy, low cholesterol diet, vit. B with C, Lipocaps, 3, q.i.d., Thiamine, 50 mg. b.i.d.</td>
<td>No relief of leg pain. Subsequent amputation of left lower extremity. Ulcer on right foot disappeared, extremity no longer painful.</td>
</tr>
<tr>
<td>RVA</td>
<td>64820</td>
<td>Male</td>
<td>RST 0.5°</td>
<td>1.0°</td>
<td>60 mg. t.i.d.</td>
<td>Low cholesterol diet, Lipocaps, 3, t.i.d.</td>
<td>Stops aching in legs that formerly kept him awake.</td>
</tr>
<tr>
<td>HMe</td>
<td>58 yrs.</td>
<td>Male</td>
<td>RST 11.0°</td>
<td>9.5°</td>
<td>30-60 mg. h.s.</td>
<td>Thyroid Ext. 16 mg. Low cholesterol diet, Lipocaps 3, t.i.d.</td>
<td>Feet still cool at night but less than formerly.</td>
</tr>
<tr>
<td>HGP</td>
<td>36 yrs.</td>
<td>Male</td>
<td>RST 9.5°</td>
<td>7.5°</td>
<td>60 mg. t.i.d.</td>
<td>Lipocaps, 2, t.i.d.</td>
<td>Pain in legs relieved except when out of drug for short time. Feet warmer to touch.</td>
</tr>
<tr>
<td>CDF</td>
<td>Male</td>
<td>RST 3.0°</td>
<td>1.0°</td>
<td>60 mg. t.i.d.</td>
<td>Lipocaps, 2, t.i.d.</td>
<td>No relief of calf pain or sores, right leg. Subsequent amputation right leg.</td>
<td></td>
</tr>
<tr>
<td>TLP</td>
<td>48253</td>
<td>Male</td>
<td>RST 8.5°</td>
<td>3.0°</td>
<td>60 mg. t.i.d.</td>
<td>Diabetic regime</td>
<td>Given warmth in feet. When not taking drug, legs not good and sleeps poorly.</td>
</tr>
<tr>
<td>JGN</td>
<td>50 yrs.</td>
<td>Male</td>
<td>RST 8.0°</td>
<td>8.0°</td>
<td>30 mg. 3-4 times/day</td>
<td>Lipocaps, 3, t.i.d.</td>
<td>No further pain; leg and foot improved.</td>
</tr>
<tr>
<td>GFS</td>
<td>57</td>
<td>Male</td>
<td>RST 8.0°</td>
<td>8.0°</td>
<td>30-60 mg. 3-4x/d for 3 mos.</td>
<td>Lipocaps, 2, t.i.d., left lumbar sympathectomy</td>
<td>Feet better; no longer cold after 8 months. Leg pain when out of drug temporarily, improving with reinstitution.</td>
</tr>
</tbody>
</table>

Arteriosclerotic Peripheral Vascular Disease with Sudden Thrombus Formation

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Temperature</th>
<th>Studies</th>
<th>Dosage and Duration</th>
<th>Simultaneous Therapy</th>
<th>Subjective and Objective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>WDM</td>
<td>100650</td>
<td>Male</td>
<td>RST 0.5°</td>
<td>5.0°</td>
<td>60 mg. q.i.d. for 4 mos.</td>
<td>Low cholesterol diet, Lipocaps, 3, t.i.d., B complex with C, Thyroid 32 mg./d. Left lumbar sympathectomy</td>
<td>Relieved for several months. Subsequent acute occlusion involving left foot with eventual amputation of both legs.</td>
</tr>
<tr>
<td>HJW</td>
<td>52 yrs.</td>
<td>Male</td>
<td>LIT 2.5°</td>
<td>7.0°</td>
<td>60 mg. q.i.d. for 2 mos.</td>
<td>Low cholesterol diet, Vit. B with C, Lipocaps, 2, t.i.d.</td>
<td>Feet staying comfortable. Feet staying warm.</td>
</tr>
</tbody>
</table>
### GROUP III—Thromboangiitis Obliterans

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Temperature Studies</th>
<th>Dosage and Duration</th>
<th>Simultaneous Therapy</th>
<th>Subjective and Objective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANT</td>
<td>63</td>
<td>Male</td>
<td>R1T 8.5, R5T 6.0, L1T 5.5, L5T 6.5</td>
<td>120 mg. q.i.d. for 4 wks.</td>
<td>Low salt diet, Vit. B with C</td>
<td>Fingers and toes remaining warm while on drug. Draining ulcer under L5T granulating while on drug; enlarged when discontinued therapy due to nausea.</td>
</tr>
<tr>
<td>IAH</td>
<td>40</td>
<td>Male</td>
<td>R1T 8.5, R5T 6.0, L1T 9.5, L5T 11.5</td>
<td>120 mg. q.i.d. for 10 mos.</td>
<td>Thiamine 50 mg. t.i.d. Vit. B with C</td>
<td>Relief of pain in right foot, but no subjective warming of that foot. Ulcer tip of R1T healed approximately 30 days. Evidence, also, of new nail growth.</td>
</tr>
<tr>
<td>JMc</td>
<td>41</td>
<td>Male</td>
<td>L1T 1.0, L5T 0</td>
<td>30-60 mg. t.i.d., p.r.n., for pain in foot—2 mos.</td>
<td>None</td>
<td>No benefit. Went on to gangrene right leg.</td>
</tr>
</tbody>
</table>

### GROUP IV—Miscellaneous

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Temperature Studies</th>
<th>Dosage and Duration</th>
<th>Simultaneous Therapy</th>
<th>Subjective and Objective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAG</td>
<td>56</td>
<td>Female</td>
<td>No temperature studies</td>
<td>60 mg. t.i.d., for 1 mo.</td>
<td>None</td>
<td>Helping aches in arm and coccyx.</td>
</tr>
<tr>
<td>AHA</td>
<td>58</td>
<td>Female</td>
<td>No temperature studies</td>
<td>30-120 mg. t.i.d. for 2 mos.</td>
<td>Reduction diet, Vit. B with C, Thiamine 50 mg. b.i.d., local heat</td>
<td>Back pain relieved.</td>
</tr>
<tr>
<td>MJMc</td>
<td>31</td>
<td>Female</td>
<td>R1T 8.5, R5T 10.0, L1T 8.5, L5T 0.5</td>
<td>60 mg. q.i.d. for 12 days</td>
<td>Sympathectomy prior to therapy</td>
<td>Relief of aching and redness. &quot;Doing well.&quot;</td>
</tr>
</tbody>
</table>

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* See footnote on page 488.
varying in age from 46 to 83 years. Diagnosis was made on the following criteria: usually 40 years of age or older, limited to lower extremities, absent peripheral pulsations, duration two to three years or less, blood cholesterol 220 mg. per 100 ml. or higher, Gofman Sf 10–20 molecules 35 mg. per 100 ml. or above and Sf 20–100 molecules 55 mg. per 100 ml. or more, calcification of the blood vessels of the leg when present (absence not excluding), evidence of atherosclerotic changes elsewhere (coronaries, brain, xanthoma palpebrarum), usually, but not always, pain, blanching, intermittent claudication, dependent rubor and prolongation of return of color on return of foot to heart level after elevation of the foot for 30 seconds. Two patients of this group suffered arterial occlusion by thrombosis secondary to arteriosclerosis. PEK, 114578, was included in this group because of the x-ray evidence of calcification and elevated blood concentration of cholesterol and Gofman molecules,* but one is forced to make a diagnosis of Raynaud's disease of unknown cause to explain changes in upper extremities.

Group III is composed of three patients with the diagnosis of thromboangiitis obliterans, all being males, aged 40, 41 and 63 years. Criteria for diagnosis in this group were: age, combined involvement of hands and feet and obliteration of peripheral pulsations. Symptoms and physical examination were otherwise essentially the same as those of arteriosclerosis; there was an absence of elevated blood cholesterol and of calcification of the blood vessels of the legs.

Group IV is composed of seven females ranging in age from 21 to 50 years with miscellaneous disorders varying from anxiety to acute pancreatitis.

Prior to administration of Regitine† orally on a therapeutic basis, an attempt was made to ascertain first the effect of the drug on the peripheral circulation of the patient by skin temperature studies. Since both vasospasm and organic occlusion are usually present in peripheral vascular disease, both the degree of occlusion and the probable degree of effectiveness of a vasodilator drug in overcoming the vasospasm can be determined by measurement of the increased skin temperature consequent to an augmented rate of delivery of heat to the skin resulting from the increase in cutaneous blood flow produced by the vasodilator drug. Records of the cutaneous temperature were made with an 8-point Leeds and Northrup micromax using iron constantin thermocouples attached to the skin with a drop of collodion. During the study, the patients were placed in a room, the temperature of which was maintained at 19 to 20 C. The cutaneous areas to be measured were exposed to the room air and care was taken to avoid contact or close approximation of any objects which might prevent rapid circulation of air past the exposed parts. Temperatures were recorded usually over the forehead, index and fourth fingers, great and little toes, together with the room temperature. Blood flow and vasoconstriction were estimated from the relationship of the temperature of the skin to that of the room and forehead temperatures. Minimal blood flow due to maximal vasoconstriction was considered to be present when the skin temperature approximated room temperature and maximal blood flow due to maximal vasodilation when the skin temperature approximated or exceeded the forehead temperature. Regitine was injected intravenously over a 30 minute period in amounts up to 0.5 mg. per kilogram, dissolved in 250 ml. of normal saline; the total amounts given varied from 20 to 50 mg.

In a further attempt to correlate the predicted response to Regitine with the actual therapeutic response, additional temperature studies were done using Etamon (TEA),‡ as it was felt that the fraction of effectiveness of Regitine to Etamon may represent the expected response as compared with full release of vasospasm by Etamon. These studies were carried out on 18 of the patients, the records of which are included in table 1. Etamon was injected under the same conditions as was Regitine, in the amount of 15 to 20 mg. per kilogram dissolved in 250 ml. of normal saline. The maximum dosage used was 1,732 mg. and the minimum was 645 mg.

For administration to the patients for evaluation of therapeutic response, Regitine was given orally and on an individual basis for each patient. Dosage and duration of trial are recorded in table 1, the dosage varying from as little as 30 mg. once a day to a maximum of 120 mg. four times a day, before or after meals, depending upon side effects. The maximum duration of trial was 14 months and the minimum was two weeks.

Simultaneous therapy is recorded for each patient in table 1 in order that no factors be overlooked which might affect the clinical response to Regitine. Evaluation of response to the drug was, of necessity, purely subjective in the majority of patients, though in some, subsequent healing of previously chronic lesions, healthier nail growth and increased walking distance afforded objective evidence of benefit. Both subjective and objective responses to the drug are recorded in table 1.

Pertinent accessory clinical findings were recorded,

* Gofman molecule (lipoprotein) determinations were done by Belmont Medical Laboratories, Inc., Belmont, Calif.
† The oral and intravenous preparations were kindly supplied by Dr. F. L. Mohr of Ciba Pharmaceutical Products, Inc., Summit, N. J.
‡ Kindly supplied by Dr. E. C. Vonder Heide of Parke, Davis and Company, Detroit 32, Mich.
EFFECTS OF REGITINE

Fig. 1. Temperature changes in the fingers of LBM, 130193, in response to 29.7 mg. (0.5 mg. per kilogram) of Regitine. Her complaint was recurring pain in the fingers of the right hand upon exposure to cold. Her diagnosis was primary Raynaud's phenomena. This response was considered a good one and the patient obtained a good response to oral administration. (See also table 1.)

*TABLE 2.—Predicted Response on Basis of Comparison with TEA or of Unaffected Part*

<table>
<thead>
<tr>
<th>Group</th>
<th>Good Response</th>
<th>Fair Response</th>
<th>Equivocal</th>
<th>No Temperature Study</th>
<th>Poor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>RLP-LBM-FIF</td>
<td>LNJ-KWL-SRW</td>
<td>MMP-ECD</td>
<td>SAG-MLG-CHM-AHW</td>
<td>MPP-RSH</td>
</tr>
<tr>
<td>II</td>
<td>PEK-DHO-TLP-RWS</td>
<td>RVA-HG-Me-HJW-EAH</td>
<td>JGN</td>
<td></td>
<td>JPT-HGP-CDF-GFS-WDM</td>
</tr>
<tr>
<td>III</td>
<td>ANT-IAH</td>
<td>GBF-NM</td>
<td></td>
<td></td>
<td>JMMe</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Temperature changes in the right and left great toes and right middle finger of JPT, 113336, in response to 30.6 mg. (0.5 mg. per kilogram) of Regitine. His complaints were those of intermittent claudication and swelling of the lower extremities. His diagnosis was arteriosclerotic peripheral vascular disease. This response was considered a poor one and the patient experienced neither subjective nor objective improvement with oral administration of the drug. (See also table 1.)

*TABLE 3.—Results of Regitine Therapy*

<table>
<thead>
<tr>
<th>Group</th>
<th>Objective Evidence of Improvement</th>
<th>Subjective Improvement</th>
<th>Equivocal</th>
<th>No Follow Up</th>
<th>No Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>LNJ-RLP-LBM</td>
<td>RLP-LNJ-LBM-RSH-KWL</td>
<td>MMP-MPP-FIF</td>
<td>SRW</td>
<td>ECD</td>
</tr>
<tr>
<td>II</td>
<td>PEK</td>
<td>HGP-PEK-DHO-HG-Me-TLP-GF-RWS-HJW-EAH</td>
<td>RVA-CDF</td>
<td>JPT-WMD-JGN</td>
<td>JMMe</td>
</tr>
<tr>
<td>III</td>
<td>ANT-IAH</td>
<td>ANT-IAH</td>
<td></td>
<td>MLG</td>
<td>GBF-MJMMe</td>
</tr>
<tr>
<td>IV</td>
<td>SAG-CHM-NM</td>
<td>AHW</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
both for substantiation of the diagnosis and for
determination of the effect upon any blood ele-
ments as previously reported by Hecht and
Crandall. An attempt was made to obtain hemo-
globin, white blood cell count and differential white
blood cell determinations before and after begin-
ing therapy with Regitine on as many patients as
possible.

In order to predict the response of a given patient
to the therapeutic trial with Regitine, the degrees
rise in skin temperature of the part above room
temperature was used as an index to the extent to
which intravenous Regitine overcame the maximal
vasoconstriction of the part obtained as described
above. This was also a measure of the amount of
vasospasm present in the particular disease process,
and in those in whom little or no increase in skin
temperature of the affected part occurred, a similar
poor response was predicted in the therapeutic trial.
Figure 1 illustrates a good response in skin tempera-
ture study, and figure 2 illustrates a poor response.
Table 2 summarized the predicted responses for the
individual patients and by groups, based on the
abstracted skin temperature studies recorded in
table 1.

Results

The responses actually obtained by the
individual patients are recorded in table 1 and
summarized in table 3, again on an individual
and group basis. Simultaneous therapy, par-
ticularly sympathectomy, must be considered in
an evaluation of results. There were five
patients who underwent sympathectomy prior
to use of Regitine, two during the course of
treatment with Regitine, and one was done
after Regitine was discontinued. It was neces-
sary to stop Regitine on the latter patient,
ANT 20211, because of an episode of acute
vasomotor collapse. It is to be noted that in
only one patient, MMP, 113539, of the Ray-
naud’s disease group, was sympathectomy done
and this was prior to Regitine trial. The two
patients undergoing sympathectomy during
their trial on Regitine were both in the arterio-
sclerotic group: WMD, 100950, had suffered
sudden thrombus formation; poor response
was predicted, of course, and subsequent
amputation was necessary. The other, PEK,
114678, underwent sympathectomy because it
was necessary to discontinue the drug therapy
since he developed a rash while taking the drug.
A good response to Regitine had been predicted
from the temperature studies and had been
obtained with the drug; the response to symp-
athectomy was satisfactory.

Correlation between the predicted and actual
responses obtained was fairly good, but in
several cases it was not possible to obtain a
follow-up and these cannot be considered in
the evaluation of the drug.

When studied by disease groups, approxi-
mately 58 per cent of the arteriosclerotic
group was predicted to get fair to good response
and obtained objective and/or subjective
response in approximately 64 per cent. This
represents a much higher percentage than
would be anticipated from the nature of the
disease. The Raynaud group, in whom good
results might be anticipated, showed 63 per
cent good or fair predicted responses, and 50
per cent showed comparable actual response.
The results in the thromboangiitis group were
encouraging, though the size of the group was
too small to be of any value in the evaluation
of the drug in this disease. The results obtained
in group IV were variable as might be antici-
pated from the assortment of diagnoses,
and temperature studies were not obtained
on four of the seven. However, a fair response
was predicted for two patients of this group,
GBF 3812 and NM 5869, both of whom had
chronic thrombophlebitis, but only one showed
subjective improvement on Regitine therapy.

In a comparison of the vasodilating effect
of Regitine and Etamon, it was found that 10
patients responded with higher average skin
temperatures, in parts tested, to Etamon than
to Regitine. Of this group, four were in the
Raynaud group, three were in the arterio-
sclerotic group, two had chronic thrombo-
phlebitis and one was in the thromboangiitis
group. The response to Regitine was greater
in five, and the two drugs produced essentially
the same amount of skin temperature rise in
three. Four of the five who showed a better
response to Regitine were in the arteriosclerotic
group, and of the two who obtained essentially
equal responses, one was in the arteriosclerotic
group, the other was in the thromboangiitis
group.

Side effects noted during the therapeutic
trial with Regitine are listed below in order of
frequency of occurrence. The frequency was
calculated as the percentage of patients experiencing a particular side effect, with many experiencing several of the reactions. It was necessary for seven of the patients to discontinue the drug entirely due to side effects. The total number of patients was 34.

Diarrhea......................... 26%
Nasal stuffiness.................. 24%
Dizziness.......................... 24%
Nausea............................. 18%
Weakness........................... 6%
Vomiting........................... 6%
Palpitation........................ 6%
Chilliness.......................... 6%
Nervousness........................ 6%
Dyspnea............................ 6%
Vasomotor collapse................ 6%
Drowsiness......................... 3% (1 patient)
Itching sensation deep in volar surface of forearm............. 3% (1 patient)
Petechial rash........................ 3%
Total incidence of side effects: 62%

Vasomotor collapse, the only side effect of any magnitude, occurred in two patients, ANT, 20211 and WDM, 100950. It occurred within a few minutes in one and approximately two hours in the other after administration of 60 mg. of the drug orally (the former was about three hours, the latter, approximately 30 minutes postprandial). The reaction was preceded by nausea and vomiting, and was then manifested by apprehensiveness, a sudden temperature elevation to 100° to 101° F. with a shaking chill, pallor, cold and clammy skin, blood pressure drop (from 140 mm. Hg systolic over 84 mm. Hg diastolic to 80 systolic over 70 diastolic in one, and from 180 systolic over 90 diastolic to 110 systolic over 80 diastolic in the other), and was followed by weakness and diarrhea. Both of the patients were in the hospital at the time of occurrence, and the reactions were successfully managed by Trendelenberg position and intravenous glucose, with full recovery and return of blood pressures to former levels in three to four hours. A blood sugar determination done on ANT, 20211 prior to administration of intravenous glucose was reported as 99 mg. per 100 cc. There was no change in any aspect of the hemogram.

DISCUSSION

The ability of Regitine to produce cutaneous vasodilation in animals and in normal students has been confirmed in this study on patients. This effect is probably produced by blocking the sympathetic constrictor impulses and in this respect is somewhat less effective than Etamon. However, correlation between the response predicted by study of the intravenous administration of Regitine and that obtained on oral administration appears to be good in the individual patient, but contradictory for the disease groups. It would be anticipated from the nature of the disease and pharmacologic properties of Regitine, that patients with Raynaud's disease would get better response than those with occlusive disease. However, percentage-wise the actual response of the Raynaud group was much poorer than either the arteriosclerotic or thrombanoangiatic groups. It is interesting to note also that all but one of the patients who got a better or equal response to Regitine in comparison with Etamon, were in the arteriosclerotic group. An explanation of these somewhat paradoxical results would be difficult, but would seem to justify further study.

In a comparison of the subjective and objective effects of Regitine and those reported for Priscoline by Grimson and colleagues in 1948,6 it appears that Regitine is somewhat inferior to Priscoline in its effects upon patients with Raynaud's disease. On the other hand the results with Regitine were more encouraging than those with Priscoline in patients with arteriosclerotic peripheral vascular disease and those with thrombanoangiatic obliterans. Responses in the miscellaneous group of patients were equivocal in both studies. Though no frequency of side effects was reported for Priscoline, our own experience with this drug indicates that many patients complain severely of chilliness, pruritis of the scalp, pilomotor reactions, conjunctival injection and gastrointestinal reactions. Those experienced with Regitine are apparently significantly less than those of Priscoline with the exception of the vasomotor collapse occurring in two patients receiving Regitine, and a mild petechial rash seen in one patient. No significant changes in white blood counts have been noted by us during prolonged therapy with either Regitine or Priscoline.

In analyzing the two cases of vasomotor
collapse, it is difficult to explain the occurrence in these two patients and yet in none of the others. Less marked symptoms of hypotension were reported in a fairly large percentage of patients. Trapold and Warren have attributed reactions to Regitine to a lowering of the blood sugar level. However, the blood sugar determination done on one of the patients experiencing the vasomotor collapse was within normal limits for what was essentially a three hour postprandial level, and though there is no record of a previous determination there was no evidence of preceding hyperglycemia. The blood pressures in the two showed the typical wide pulse pressures of arteriosclerosis; the drop was predominantly systolic, suggesting a sudden reduction in stroke volume output by the heart. It is of significance that each subject had previously been taking the drug for several days before the reactions were first noted; in other words, a sensitivity seemed to have developed after prolonged use of the drug.

It seems that there is no way of predicting such a reaction, or preventing it by regulating administration by meals or otherwise. However, it is easily managed by Trendelenberg position, intravenous glucose, the glucose being recommended on the basis of the earlier study referred to above, and, of course, discontinuance of the drug.

It is concluded that a trial on Regitine therapy is indicated before resorting to sympathectomy in any peripheral vascular disease as only three patients in this study underwent sympathectomy during or after Regitine therapy, and treatment has been maintained as long as fourteen months. It is a valuable adjunct after sympathectomy, and in the dose range of 30 to 60 mg. two to four times a day is tolerated with relatively few serious side effects in the majority of patients.

**Summary**

1. Regitine, a new antiadrenergic drug, has been shown to have both adrenolytic and sympatholytic properties; its ability to relieve vasospasm induced by cold being approximately equal to that of Priscoline. This paper deals with the clinical trial of Regitine, felt to be justified by previous studies.

2. Thirty-four patients were studied: 10 with Raynaud’s disease, 14 with arteriosclerotic peripheral vascular disease, three with thromboangiitis obliterans and seven with miscellaneous diagnoses.

3. The patients were first tested with Regitine intravenously while skin temperatures were recorded, in order to ascertain the effect of the drug on the peripheral circulation of the patient. The response shown, and, in many cases, compared with a skin temperature study with Etamon, was used to predict the therapeutic response to Regitine.

4. Regitine was administered orally in doses ranging from 30 mg. once a day to 120 mg. four times a day. The maximum duration of trial was 14 months and the minimum was two weeks. Evaluation of the response was largely subjective, but in many, objective evidence was present.

5. Correlation between the predicted and the actual response obtained was good in the individual patient, but contradictory for the disease groups. Thus, the patients in the arteriosclerotic group appeared to obtain more benefit from the oral administration of the drug than did the Raynaud group. Results in the thromboangiitis group and in one patient with chronic thrombophlebitis were encouraging.

6. Serious side effects were few, the only reaction of any magnitude being vasomotor collapse which occurred in 2 of the 34 patients receiving the drug; however, minor side effects were noted by 62 per cent of the patients.

7. Regitine appears to be a useful adjunct to treatment of peripheral vascular diseases and is felt to be indicated prior to consideration of sympathectomy. Furthermore it is useful in subsequent treatment of cases which have undergone sympathectomy.

**Sumario Español**

Este es un estudio de los efectos clínicos de Regitine, una nueva droga anti-adrenérgica, las propiedades farmacológicas de la cual son similares a las de Priscoline. Treinta y cuatro pacientes, cuyos diagnósticos entran en el grupo de enfermedades periféricas vasculares, y en un grupo misceláneo se les administró la droga intravenosamente y los resultados fueron estudiados mediante determinaciones de temperatura.
Efectos de Regitine cutánea en un atentado a predecir el resultado terapéutico al administrar Regitine. La droga fue luego administrada oralmente por intervalos variables de tiempo con evidentes resultados subjetivos y objetivos al igual que efectos secundarios no deseados que también fueron observados. Los resultados de estas observaciones se presentan en este trabajo.

REFERENCIAS


Effects of Regitine (C-7337) in Patients, Particularly Those with Peripheral Arterial Vascular Disease

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