An Evaluation of the Ability of Priscoline, Regitine, and Roniacol to Overcome Vasospasm in Normal Man

Estimation of the Probable Clinical Efficacy of these Drugs in Vasospastic Peripheral Vascular Disease

By Harold D. Green, M.D., W. Kenneth Gobel, Michael J. Moore, M.D., and Thomas C. Prince, M.D.

This paper is a study of the comparative efficacy of Priscoline, Regitine, and Roniacol in relaxing vasospasm in the extremities of normal human subjects. A total of 60 studies were performed on 14 subjects. Severe cutaneous vasospasm was induced by exposure of the lightly clad subject to an environmental temperature of 20 C for one hour or more. In half the tests the severe vasospasm was reduced to moderate vasospasm by application of heat to the torso of the chilled subjects. The effectiveness of the drugs was tested by giving them by intravenous infusion after the appropriate state of vasospasm had been obtained. The degree of relaxation of vasospasm was estimated from the resulting changes in cutaneous temperature recorded with thermocouples.

In each of the peripheral vascular disease entities, the vasomotor component varies. Thromboangiitis obliterans exhibits a decreasing vasospastic element as the organic occlusive element increases. In Raynaud's phenomenon and allied conditions, however, the vasospastic element predominates. Some vasoconstriction is often present in arteriosclerosis. The usage of drugs which abolish vasospasm is, therefore, a helpful adjunct in determination of the degree of vasospasm, in differentiation of the disease entities, and in the treatment of disease where vasoconstriction plays a part in the presenting symptoms.

In previous papers usage of such agents in the evaluation of the degree of vasospasm has been discussed. This paper presents a method for estimating the probable clinical effectiveness of drugs designed to relax vasospasm. In principle, a reproducible degree of vasospasm is induced in normal subjects and the ability of the drug to overcome this vasospasm is tested.

The ideal therapeutic agent for this disease group would be one which induced maximal vasodilation in the extremities with minimal untoward side effects. In this paper we will consider three agents and compare the results of their trial upon normal subjects. These agents are: (1) Priscoline, (2) Regitine, (3) Roniacol. The chemical formulas for these drugs are:

Priscoline, 2-benzyl-4,5-imidazoline HCl.

\[
\text{Priscoline, } 2\text{-}[N\text{-p'-} tolyl\text{-N-(}m\text{'-hydroxyphenyl)}\text{-} \text{aminomethyl}\text{-} \text{imidazoline}.
\]

Regitine (C-7337) 2-[N-p'-tolyl-N-(m'-hydroxyphenyl)-aminomethyl]-imidazoline.

\[
\text{Regitine, } 2\text{-}[N\text{-p'-} tolyl\text{-N-(}m\text{'-hydroxyphenyl)}\text{-} \text{aminomethyl}\text{-} \text{imidazoline}.
\]

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* Kindly supplied by Ciba Pharmaceuticals, Inc., Summit, N. J.
† Kindly supplied by Hoffmann-La Roche, Nutley, N. J.
Regitine, like Priscoline, has slight inherent vasodilator effect but possesses the ability to convert the normal epinephrine vasoconstriction into vasodilation. When given intra-arterially in a dog, approximately 0.15 mg. per kilogram of Regitine is necessary to completely reverse the action of 1 μg. of epinephrine given intra-arterially. Under similar conditions, 2 mg. per kilogram of Priscoline are required to reverse the action of 1 μg. of epinephrine.

**METHODS**

The method of recording the cutaneous temperature is discussed in more detail, both in validity and mechanics of the method, in previous papers.\(^1\)\(^2\) In all cases, skin temperature was recorded with thermocouples held firmly in contact with the skin by a strip of adhesive, placed about 0.5 cm. proximal to the tip of the couple. In the earlier portion of this study, the skin temperature was recorded on an 8-point Leeds and Northrup Micromax using iron constantin thermocouples (recording time, one minute per point). In the latter portion of the experiment we used a 12-point Brown potentiometer with copper constantin thermocouples (recording time 12 seconds per point).

The subjects were placed in a recumbent position during the study, clad only in undershorts or slips, in a room the temperature of which was kept at approximately 20°C. Individual variants from this temperature are noted in table 1. The temperatures were procured from the right and left third and fourth fingers in the series without body warming, from the index and fourth fingers of the right and left hand in the series with body warming. The lower extremity leads were from the right and left great, middle, and small toes, in both series. Minimal blood flow due to maximal vasoconstriction was considered to be present when the skin temperature approximated the room temperature, and maximal blood flow due to maximal vasodilation when the skin temperature approximated the forehead temperature. Table 1 shows the range of individual forehead temperatures during the respective periods of drug administration. A strong vasoconstriction in the lower extremities and a moderate vasoconstriction in the upper extremities was induced by an initial one to one and a half hour exposure in the constant temperature room. This is illustrated in figures 1 and 2 in the control period prior to the drug infusion, or heating, respectively.

Two methods were followed in the evaluation of the three drugs. These were: (1) administration of the drugs without body warming, (2) administration of the drugs during a period of body warming. The subjects were normal medical students. Ten students received each of three drugs in the first series without body warming. The second study used six of the original subjects and four new individuals; these 10 students were subjects to all three drugs in the body warming series. Each student had his temperature taken previous to the study, and was excluded if febrile. The students did not eat during nor for four hours prior to the experiment.

1. After approximately an hour of body cooling, the ten subjects received either Priscoline, Regitine, or Roniacol. In each case the agent was dissolved in 200 ml. of 0.9 per cent saline and administered by infusion over a period of approximately one half hour. Arterial pressure was checked every five minutes during the infusion and until it stabilized after completion of the infusion. The drugs were given in the following dosage: Regitine 0.5 mg. per kilogram, Priscoline 2.0 mg. per kilogram, and Roniacol 3 mg. per kilogram. Following completion of the infusion the student was retained for at least a half hour recording period; in event of suggestion of further changes the temperatures were recorded until the majority of readings were stabilized.

2. Ten subjects received a combination of body warming plus Priscoline, Regitine or Roniacol, in the above dosages. The period of body warming was preceded by a period of cooling until the temperatures of the extremities approximated room temperature. The body warming was accomplished by heating pads, placed in contact with the back and front of the chests, with one wool blanket covering the torso, and with the extremities exposed. The duration of body warming prior to the drug administration averaged 45 minutes. An effort was maintained to reach maximal vasodilatation by heating, regardless of the duration. At the completion of this body warming period, the infusion was instituted while maintaining warming of the body. Temperatures were recorded until the majority of leads stabilized.

**RESULTS**

1. *Effects of Drugs without Body Warming.* Paired points on the left and right extremities never differed more than 1°C. The data presented is all for the left extremities. It had been noted in previous studies that the tips of the digits and toes demonstrated the most marked vasomotor changes.\(^3\) The finger, great
and small toes were chosen, therefore, to represent the thermal responses to the drugs. Figure 1 demonstrates the response of 10 individuals to Priscoline, Regitine, and Roniacol without body warming. The range of the room and forehead temperatures during each study, and the month of the year of the study is presented under the appropriate heading in table 1, part A. In the figure, line 1 represents mean room temperature, line 2 represents mean forehead temperature.

a. Priscoline. The range of control tempera-

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<th>Date</th>
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Mean: 20.2 31.1 20.1 31.2 20.1 30.4

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Mean: 20.6 31.1 20.6 30.9 20.2 30.9

Part A. Subjects are identified on figure 1 by symbols A to J. The same subjects are used in all 3 studies.

Part B. Subjects are identified on figure 2 by symbols A to J. Six of the subjects in this series are from previous series without body warming (*). Four new subjects were used. All 10 subjects are used in all three studies.

Date column denotes month each individual study was run. Room column denotes the range of room temperature during each study, mean is given at the end of each column for that particular column.

Forehead column denotes the range of forehead temperatures of each study, mean also is given at the bottom of the column.
toe rose in six subjects and remained unchanged in four. An increased temperature in the little toe was noted in seven subjects, the temperature remained unchanged in three. This drug caused moderate vasodilation in the fingers and toes. This moderate response is shown in the average temperatures (table 2, column B).

Systolic arterial pressure fell 14 mm. Hg in one subject and rose 15 mm. Hg on another occasion; diastolic arterial pressure fell 10 mm. Hg on one occasion. In the remainder the pressures remained stable. Side effects noted were chills and shivering during and after the experiment, flushing of the head and neck, and a slight feeling of giddiness for a short period subsequent to the experiment.

b. Regitine. Regitine, second row of figure 1, exhibits essentially the same picture as Priscoline. The maximal temperatures reached, after giving the drug, are slightly less than those of Priscoline (table 2, column D). The finger temperature increased in six subjects and remained unchanged in four. In four subjects the temperature of the great toe increased, in one subject it decreased, and, one subject demonstrated an initial decrease during the infusion followed by an increase. The left little toe exhibited five increases in temperature and in five subjects the temperature remained essen-

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**Fig. 1.** Graphs of responses to Priscoline, Regitine and Roniacol of 10 normal medical students in whom severe vasospasm was induced by chilling for one or more hours. Top row of graphs: responses to Priscoline (2.0 mg. per kilogram); middle row: responses to Regitine (0.5 mg. per kilogram); bottom row: responses to Roniacol (3.0 mg. per kilogram); first column: responses in left middle finger; second column: responses in left great toe, third column: responses in left small toe; broken line (1) represents average room temperature, broken line (2) represents mean forehead temperature. In each graph the segment to the left of the arrow gives the temperature during the period of chilling required to induce the vasospasm. The segment to the right of the arrow gives the responses to the drug. For additional data see table 1 (A) and table 2.
tionally unchanged. One subject, GB, demonstrated a moderate response to Regitine, but responded poorly to Priscoline and Roniacol. This drug caused a slightly smaller vasodilation in the hand and about the same vasodilation in the toes as was seen with Priscoline.

Both systolic and diastolic arterial pressure fell on the average 5 mm. Hg. No dramatic increases or decreases were noted. Side effects noted were nasal congestion in all subjects, with but few exceptions flushing of the face, and in a few subjects a metallic taste.

c. **Roniacol.** The range of control temperatures for Roniacol is depicted in the third row of figure 1. The average temperatures are shown in table 2, column E; they are slightly less in the fingers and toes after giving the drug than the control temperatures. In one subject the finger temperature decreased at the commencement of the infusion but rose significantly prior to completion of the infusion; in five subjects no distinct effect of the drug was noted; in four subjects an accelerated drop in finger temperature accompanied the drug infusion. In the left great toe Roniacol caused a very slight increase in one case, an accelerated decrease in temperature in three subjects and essentially no change in six subjects. No significant increase in skin temperature was noted in the left small toe in any subject subsequent to drug infusion. Eight subjects remained stable and three dropped slightly subsequent to the drug injection. A typical finding is that of BG (G) who showed a moderate increase in temperature in response to Priscoline and Regitine but none to Roniacol. AC (A) demonstrated a poor response to all three agents. GB (C) responded well to Regitine but poorly to Priscoline, KB (D) responded well to Priscoline but poorly to Regitine; both responded poorly to Roniacol.

A fall of 20 mm. Hg was noted on one occasion in both systolic and diastolic arterial pressure; on one occasion a decline of 10 mm. Hg systolic pressure was observed, and upon another occasion a 16 mm. Hg fall in diastolic arterial pressure. The arterial pressure, however, generally maintained a steady level in the remaining subjects during the drug injection. Side effects noted were minimal. Several subjects noted a sense of warmth and one noted epigastric pain of a mild nature.

2. **Effects of Drugs with Body Warming.** Figure 2 presents the graphic representation of the temperature changes with body warming plus Priscoline, Regitine or Roniacol. Table 1, part B, gives the range and average room and forehead temperatures and the month each drug was studied on the individuals. Line 1 of figure 2 is the mean room temperature and line 2 is the mean forehead temperature. Table 2 exhibits the average temperatures during the body-warming experiment. Columns H, K, and N disclose the augmenting effect of body

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**Table 2.** Summary of Average Temperatures of Figures 1 and 2

<table>
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<tr>
<th>Without Body Warming</th>
<th>With Body Warming</th>
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<tr>
<td></td>
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<td></td>
<td>Control</td>
</tr>
<tr>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Left index finger</td>
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<td>Left great toe</td>
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<tr>
<td>Left small toe</td>
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*Control* is taken at the point on the graph immediately before the drug infusion in the series with body warming, and the point immediately prior to body warming in the series with body warming. In the Roniacol series the control temperature was taken eight minutes before the drug was given due to the temporary drop in temperature which accompanied the insertion of the infusion needle (see text).

*Body warming* was taken at the point where the maximal increase in skin temperature occurred.

*Drug* is the temperature at that point where the maximal response was elicited in cases of increased temperature, and at the end of the infusion period in the case of decrease of skin temperature.
warming prior to drug administration. Body warming promoted a greater increase of blood flow to the fingers than the lower extremities in all three studies. Blood flow to the toes was increased but little by the body warming procedure in all three drug studies. The latter facts substantiate the findings reported in previous papers.3, 4

caused excellent vasodilation in both hands and feet.

The arterial blood pressures in this group were stable although a rise in two instances of 15 and 20 mm. Hg was noted. An 18 mm. Hg decrease in diastolic arterial pressure was noted in one instance. Side effects noted in order of their frequency were chilliness, cutis anserina

**FIG. 2.** Graphs of responses to Priscoline, Regitine, and Roniacol of 10 normal medical students in whom a state of moderate vasospasm was induced by chilling followed by body warming. In each graph the segment to the left of the first arrow gives the temperature during the period of chilling. The segments between the first and second arrows gives the temperatures during the period of body warming required to moderate the initial state of vasospasm; the segment to the right of the second arrow gives the temperature during the response to the drug; body warming was continued from the first arrow to the end of the graph. The break in the chart was necessitated by the differences in the lengths of the periods of body warming for the different subjects. The doses were the same as those for figure 1. For other data see figure 1 and tables 1 (B) and 2.

a. **Priscoline.** As shown in figure 2, on five subjects a further increase in temperature of the fingers occurred subsequent to the administration of Priscoline; one exhibited a slight decrease, and the remainder were essentially unchanged. All but one subject AC (F) demonstrated a considerable increase in temperature in both toes following Priscoline. The averages in table 2, column 1, demonstrate that the combination of body warming plus Priscoline (goose flesh), flushed face, burning eyes, metallic taste, tingling of the face, slight tachycardia, and heaviness of the eyelids; one subject became nauseated and vomited.

b. **Regitine.** Eight subjects exhibited an increase in finger temperature following drug administration, and two remained unchanged. Regitine produced a moderate increase in the average temperature of the fingers (table 2, column 1). All subjects demonstrated an in-
crease in temperature of both toes following drug administration. In two, KG (D) and AS (H) the maximum temperatures reached were not very high. These two subjects had responded well to Priscoline. Subject AC (F), who failed to dilate with Priscoline plus body warming, gave a good response in fingers and toes to body warming plus Regitine. In general the combination of body warming and Regitine resulted in vasodilation in the fingers and toes which was almost as satisfactory as that noted with Priscoline plus body warming (table 2, columns I and J).

Both systolic and diastolic arterial pressures rose on the average of 5 mm. Hg; nasal congestion, scleral injection with smarting, and flushing of the face were noted with the drug.

c. Roniacol. The fingers, on the average, exhibited a slight further rise in temperature following Roniacol administration. Three subjects showed no significant change in the temperature of the finger following drug administration; subject AS (H) showed a marked rise after the infusion was discontinued; three other subjects revealed a moderate increase in temperature following administration of Roniacol; one subject exhibited a marked fall during the infusion and one demonstrated a marked fall immediately after the infusion, the remaining two subjects exhibited gradual falls in the skin temperature of the finger following drug administration. A very slight increase in the average skin temperature was noted in the great toe following Roniacol administration (table 2, column O). There was one marked increase in skin temperature of the large toe with a decrease following infusion; four subjects remained stable through the procedure, and five moderate decreases in the temperature of the great toe were noted either during or after the Roniacol administration. A decrease in the average temperature was noted in the small toe following Roniacol administration. In one subject there was a slight increase in skin temperature following Roniacol; four subjects remained essentially unchanged; and in five a moderate decrease in the skin temperature of the small toe was noted. Thus it is seen that Roniacol was capable of improving the vasodilation induced by body warming in the hand, but was unable to induce effective dilation in the feet, even when combined with body warming. In this regard this drug is inferior to Priscoline and Regitine.

Systolic arterial pressure fell 10 mm. Hg in one instance, diastolic fell 10 mm. Hg in another, systolic rose 13 mm. Hg and diastolic 8 mm. Hg in another instance. However, the remainder of the arterial pressures remained stable. Side effects noted were a burning, stinging sensation of the head, face and neck, fairly painful in a few instances, flushing and tingling of the face, metallic taste, burning of the eyes, a slight headache in one case, and mild epigastric pain in another case.

In both studies (with and without body warming) no cases of orthostatic hypotension occurred upon arising, in any of the 60 individual studies.

During the series without body warming the forehead temperatures increased on the average of 1.2 C., range +0.5 to +1.5 C., during the infusion of Priscoline; the skin temperature of the forehead then either remained stable or dropped slightly after terminating the infusion. Regitine demonstrated an average decrease of 0.3 C., range −1.5 to 0 C. Roniacol showed no average change, range +1.5 to −3.0 C. Both of the latter drugs showed either a decrease or stabilization of the forehead temperature subsequent to the infusion.

The body warming procedure, per se, exhibited an average increase of 1.1 C. in the forehead temperature in the Priscoline series, range 0 to +4.0 C. This procedure in the Regitine series showed an average increase of 1.0 C., range −0.5 to +3.0 C., and the Roniacol series showed an average increase in forehead temperature of 0.5 C. with a range of −0.5 to +1.5 C.

In the series with body warming Priscoline exhibited an average increase in forehead temperature during the drug infusion of 1.0 C., range +2.5 to −1.0 C. Regitine showed an average increase in the forehead temperature of 0.1 C., range 0 to +1.0 C. Roniacol showed an average increase in forehead temperature of 1.0 C., range +2.5 to −1.0 C. In all three
DISCUSSION

It is of interest to note that the tabulated results of Priscoline in this paper demonstrate that the maximum cutaneous temperatures reached were not as great in this work as in a previous study.1 The room temperatures, in the previous studies fluctuated more than in the present study; and the air velocity in this study was 60 ft. per minute as compared with 25 to 50 ft. per minute in the previous experiments.2 These factors might well account for the differences in cutaneous temperatures noted after Priscoline in the two studies.

Priscoline and Regitine compared favorably in the series without body warming. Priscoline demonstrated a slightly better efficiency in increasing the blood flow in the finger. Priscoline also increased the temperature in the fingers and toes in a slightly larger number of subjects than did Regitine. Roniacol, in the doses used, demonstrated little ability to cause vasodilation in the absence of body warming, the increased blood flow being very meager. Roniacol in only one instance exhibited an increase in blood flow of the upper extremity, and showed no adequate increases in blood flow of the lower extremities.

It was noted that the body warming procedure, per se, was the most valuable method to promote increased blood flow in the upper extremities. In many cases maximal temperature was induced in the fingers by body warming per se; in others maximal temperature was obtained only by the combination of body warming plus a drug. Regitine plus body warming induced the highest temperatures in the finger. Priscoline plus body warming caused on the average the highest maximal temperatures in the toe; Regitine, with body warming, duplicated the beneficial results of Priscoline, but to a slightly lesser extent.

Roniacol again offered little increase in blood flow when administered with body warming. Only one subject manifested a result worthy of note. Three of the subjects demonstrated a decrease of the finger temperature subsequent to infusion, as did four in the great toe and five in the small toe. This drug in the dose used is apparently not a very effective vasodilator.

It is interesting to note that, in the series without body warming, particularly in the Roniacol series, and also occasionally in the series with body warming, a sudden decrease in skin temperature occurred immediately upon insertion of the infusion needle with usually a return to the preceding temperature 8/16 minutes after the beginning of the infusion. This change occurred in some instances in both the upper and lower extremities of the same individual in the same drug run, in other instances it occurred only in one of the extremities. The etiology of this sudden but moderate temporary decrease in skin temperature is unknown.

It is quite apparent that Priscoline and Regitine are more effective in this study in overcoming vasospasm. Priscoline offers perhaps a slightly better dilating effect than Regitine. Regitine, however, with its less unpleasant side effects is to be considered seriously. Both drugs exhibit the ability to cause increased blood flow to the extremities, and should be tested clinically for their relative efficacy of performance in peripheral vascular diseases.

While this study demonstrates the ability of Priscoline and Regitine to overcome vasospasm, the exact mechanism of action is unknown. Whether they act by blocking epinephrine or the action of sympathin at the nerve endings is unknown. However, since the effects are similar to those of spinal anesthesia, the drugs probably act at least in part by blocking sympathetic nerve impulses.

SUMMARY

1. Vasoconstriction induced by a low temperature room and vasodilation induced by drugs and by body warming have been measured on 14 normal subjects in this study. The measuring instruments were potentiometers and thermocouples.

2. The method was used to test the efficacy of the drugs in overcoming vasospasm in the normal subjects in order to evaluate the pos-
sibility of their subsequent usage in peripheral vascular diseases.

3. Severe cutaneous vasospasm was induced by exposure of the lightly clad subject to an environmental temperature of 20 C. for one hour or more. In half the tests the severe vasospasm was reduced to moderate vasospasm by application of heat to the torso of the chilled subjects.

4. Sixty individual studies were performed, 20 on each of three drugs. These drugs were Priscoline, Regitine, and Roniacol. Ten studies were performed on each drug without body warming, and 10 with body warming. Body warming was induced with two heating pads applied to the torso and covered with a blanket.

5. The drugs were administered intravenously over a period of approximately one half hour in the dosage of Priscoline 2.0 mg. per kilogram, Regitine 0.5 mg. per kilogram, or Roniacol 3.0 mg. per kilogram dissolved in 200 ml. of 0.9 per cent saline.

6. It was discovered that Priscoline and Regitine are both fairly good vasodilators especially in the upper extremities. In the series without body warming, Priscoline proved to be slightly better. Roniacol gave poor results. No dangerous or painful untoward reactions were noted with any of the agents.

7. In the body warming series it was noted that body warming, per se, gave better vasodilation in the upper extremity than any of the drugs tested. All three drugs aided slightly blood flow to the upper extremities, subsequent to body warming; the order of efficacy was Regitine, Priscoline and Roniacol.

8. Body warming, per se, proved of little use in increasing the blood flow to the lower extremities. Priscoline during body warming augmented the lower extremity flow greatly. Regitine did quite adequately also. Roniacol exhibited no significant results. No untoward side effects were observed.

9. Forehead temperatures were increased by Priscoline alone, by body warming alone, and further increased by Priscoline and Roniacol when given during body warming.

10. Comparative clinical trial of Priscoline and Regitine plus body warming is advised to further substantiate their efficacy as vasodilators in vasospastic peripheral vascular diseases involving the upper or lower extremity. Roniacol plus body warming may be effective in the treatment of vascular spasm involving only the upper extremity.

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An Evaluation of the Ability of Priscoline, Regitine, and Roniacol to Overcome Vasospasm in Normal Man: Estimation of the Probable Clinical Efficacy of these Drugs in Vasospastic Peripheral Vascular Disease

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