The Effect of Priscoline on the Clearance of Radiosodium from Muscle and Skin of Man in Normal and Diseased Limbs

By Jack Freund, M.D., Lawrence H. Wisham, M.D., and Rosalyn S. Yalow, Ph.D.

The radiosodium clearance technique was used to measure the effect of Priscoline given intravenously on the effective blood flow in muscle and skin of normal subjects and patients with peripheral vascular disease. The only clinically significant increase in the clearance rate of radiosodium (Na\(^{24}\)) occurred in the skin; the clearance rate in muscle showed small increases which were constantly present but not considered to be clinically significant.

The recent work of Kety\(^1,2\) introduced a method of indirectly measuring the effective blood flow in human muscle by determining the rate of clearance of injected radiosodium (Na\(^{24}\)). Other investigators\(^3,4\) have studied the clearance of radiosodium from the gastrocnemius muscle in normal subjects and patients with peripheral vascular disease. They concluded that the method was an additional tool in evaluating the circulatory physiology of an extremity and suggested its use in evaluating therapy.

The authors\(^5\) have previously demonstrated that the clearance rates of radiosodium from the gastrocnemius and biceps muscles in normal man were reproducible in the same individual within a significant predictable range over a period of three months.

The present study was undertaken to observe the effect of Priscoline on the clearance of radiosodium from the calf muscle and overlying skin of patients with arteriosclerosis obliterans, and individuals with normal cardiovascular systems.

Materials and Methods

The subjects for this study consisted of two groups of male patients. In the first group were patients from the Cardiovascular Section of the Medical Service with symptoms and objective findings of peripheral vascular disease. During their hospital stay, these patients were also evaluated in the peripheral vascular disease clinic where Landis-Gibbon tests\(^6\) and posterior tibial blocks were performed. The pertinent history, physical findings, and laboratory data are summarized in Table I. The subjects in the second group were male patients between the ages of 20 and 40 with normal cardiovascular systems. There were 74 studies on 14 patients with peripheral vascular disease, and 15 studies on six normal subjects. Prior to each experiment, the subject rested in the laboratory in the supine position for 10 minutes. The temperature of the laboratory was maintained between 75 and 78 F.

An isotonic solution of sodium chloride containing 3 to 5 microcuries of radiosodium per 0.1 cc. of solution was used in all experiments.

In the studies on muscle, 0.1 cc. of radiosodium solution was injected into the belly of the gastrocnemius muscle using a 20 gage, one and one-half inch needle inserted to the hilt. The skin injections were made with a 26 gage needle, raising a bleb in the skin over the calf with .03 to .05 cc. of radiosodium solution. In all the patients with arteriosclerosis obliterans except Mas, the skin and muscle studies were performed on the same limb. Immediately after all injections of radiosodium, a thin mica-window Geiger counter was placed in a fixed position\(^7\) at a 45 to 90 degree angle to the long axis of injection and counting was started. The activity was recorded, using a scaling circuit with scale selections at 16, 32, 64 and 128. An automatic printer recorded register readings at intervals of one minute for one hour during muscle determinations. Raw data at two-minute intervals were plotted on semilogarithmic paper.

In the experiments on skin, the Geiger counter was placed directly over the injection site. All subjects were advised against moving the limb being studied.
### Table 1.—Clinical and Laboratory Findings

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Limb</th>
<th>History</th>
<th>Physical</th>
<th>Oscillometries Below knee</th>
<th>Above ankle</th>
<th>Post-Tibial Blocks</th>
<th>Landis-Gibbon</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bat</td>
<td>57</td>
<td>Rt.</td>
<td>Diabetes 12 yrs.; intermittent claudication and burning feet 2 to 3 yrs.</td>
<td>Femoral pulses good; popliteal pulses questionable; foot pulses absent</td>
<td>Rt. ½ 0</td>
<td>Lt. ½ 0</td>
<td>Negative for temperature rise</td>
<td>Negative for temperature rise</td>
<td>Arteriosclerotic heart disease; arteriosclerosis obliterans; diabetes melitus</td>
</tr>
<tr>
<td>Sho</td>
<td>62</td>
<td>Lt.</td>
<td>Diabetes 20 yrs.; ulcer plantar arch rt. foot 2 to 3 mos. with pain and swelling rt. foot</td>
<td>Atrophic changes in nails bilaterally; patent femorals and lt. popliteal; other pulses absent</td>
<td>Rt. 1 0</td>
<td>Lt. 6 0</td>
<td>Negative for temperature rise</td>
<td>Negative for temperature rise</td>
<td>Diabetes mellitus; arteriosclerosis obliterans; ulcer rt. foot</td>
</tr>
<tr>
<td>McC</td>
<td>63</td>
<td>Lt.</td>
<td>Dyspnea on exertion 2 mos.; intermittent claudication (bilateral) 2 to 3 mos.</td>
<td>Both femoral and rt. popliteal pulses present; other pulses absent</td>
<td>Rt. 7 1½</td>
<td>Lt. 0 0</td>
<td>Maximal dilatation prior to procedure</td>
<td></td>
<td>Arteriosclerotic heart disease; arteriosclerosis obliterans; pulmonary emphysema</td>
</tr>
<tr>
<td>Alb</td>
<td>71</td>
<td>Rt.</td>
<td>Intermittent claudication (bilateral) 8 yrs.; burning rt. foot 1½ yrs.</td>
<td>No pulses below femorals; rt. foot mottled cyanosis</td>
<td>Rt. 0 0</td>
<td>Lt. Flicker 0</td>
<td>No significant rise in temperature</td>
<td></td>
<td>Arteriosclerosis obliterans</td>
</tr>
<tr>
<td>Fin</td>
<td>63</td>
<td>Rt.</td>
<td>Mummification of 2nd and 4th rt. toes without premonitory signs 4 mos.</td>
<td>Both femorals and popliteals present; all foot pulses absent</td>
<td>Rt. 6 trace</td>
<td>Lt. 3 trace</td>
<td>Negative for temperature rise</td>
<td></td>
<td>Arteriosclerosis obliterans</td>
</tr>
<tr>
<td>Bri</td>
<td>64</td>
<td>Lt.</td>
<td>Intermittent claudication 6 yrs.</td>
<td>Pallor of toes; lt. foot pulses absent; rt. popliteal present; popliteals and femorals normal</td>
<td>Rt. 6 2</td>
<td>Lt. 4 0</td>
<td></td>
<td></td>
<td>Cor. pulmonale; arteriosclerosis obliterans</td>
</tr>
<tr>
<td>Case</td>
<td>Age</td>
<td>Side</td>
<td>Condition</td>
<td>Findings</td>
<td>Result</td>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blo</td>
<td>51</td>
<td>Lt.</td>
<td>Intermittent claudication 4 yrs.</td>
<td>Only femorals patent BP 210/110</td>
<td>Rt. ½ Lt. 1½</td>
<td>Hypertensive and arteriosclerotic heart disease; arteriosclerosis obliterans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kle</td>
<td>60</td>
<td>Rt.</td>
<td>Above knee amputation for acute arterial occlusion Lt. lower extremity 1947; cardiac decompensation 1948</td>
<td>Rt. femoral and popliteal good; only post-tibial felt; Lt. femoral absent; rt. foot cold and cyanotic</td>
<td>Rt. 10 Lt. 0</td>
<td>Arteriosclerotic heart disease; arteriosclerosis obliterans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gre</td>
<td>56</td>
<td>Rt.</td>
<td>Diabetes 10 yrs.; 2 episodes of myocardial infarction; intermittent claudication (bilat.) 3 yrs.</td>
<td>Absent arterial pulses below femoral</td>
<td>Rt. 5 Lt. 2</td>
<td>Arteriosclerotic heart disease; diabetes mellitus; arteriosclerosis obliterans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hel</td>
<td>39</td>
<td>Lt.</td>
<td>Gangrene Lt. toe of 2 mos. duration</td>
<td>Absent Lt. post-tibial and Lt. dorsalis pedis; mumification Lt. great toe</td>
<td>Rt. 9 Lt. 8</td>
<td>Thromboangiitis obliterans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nev</td>
<td>37</td>
<td>Rt.</td>
<td>Frost bite 1942 with cold sensitivity since; persistent cyanosis ending in gangrene great rt. toe 7 wks. duration</td>
<td>No dorsalis pedis and faint post tibial on rt., both feet cold, rt. foot sweating profusely</td>
<td>Rt. 8 Lt. 9</td>
<td>Thromboangiitis obliterans with prior cold-sensitization and frost bite</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prior to the intra-arterial injections, the skin and subcutaneous tissue over the femoral artery of the ipsilateral limb were infiltrated with 1 to 2 cc. of 1 per cent procaine. Priscoline, 37.5 mg., was then injected into the femoral artery over a period of 30 seconds. Following removal of the needle, the site was compressed for 30 to 60 seconds to prevent hematoma formation. Similar pressure on non-injected subjects did not result in an increase in 75 mg. in 500 cc. of 5 per cent glucose in sterile water, was infused into the femoral artery over a period of one hour. The radiosodium was injected into the muscle two to three minutes after the infusion was started.

The time between studies on any one individual varied from one day to four months.

In all experiments the data were plotted on semilogarithmic graph paper as a function of time. As

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Clearance Constant (Minutes⁻¹)</th>
<th>Clearance Half Life (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Values</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average K Constant</td>
<td>Intra-arterial</td>
</tr>
<tr>
<td>Bat</td>
<td>57</td>
<td>.092</td>
<td>.003</td>
</tr>
<tr>
<td>Sho</td>
<td>62</td>
<td>.066</td>
<td>.066</td>
</tr>
<tr>
<td>McC</td>
<td>66</td>
<td>.066</td>
<td>.066</td>
</tr>
<tr>
<td>Alb</td>
<td>71</td>
<td>.082</td>
<td>.075</td>
</tr>
<tr>
<td>Fin</td>
<td>63</td>
<td>.051</td>
<td>.072</td>
</tr>
<tr>
<td>Bris</td>
<td>64</td>
<td>.088</td>
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<td>Blo</td>
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<td>.096</td>
<td>.068</td>
</tr>
<tr>
<td>Kle</td>
<td>60</td>
<td>.066</td>
<td>.070</td>
</tr>
<tr>
<td>Gre</td>
<td>56</td>
<td>.079</td>
<td>.075</td>
</tr>
<tr>
<td>Goe</td>
<td>41</td>
<td>.069</td>
<td>.069</td>
</tr>
<tr>
<td>Gut</td>
<td>43</td>
<td>.069</td>
<td>.069</td>
</tr>
<tr>
<td>Tho</td>
<td>51</td>
<td>.069</td>
<td>.074</td>
</tr>
<tr>
<td>Hel*</td>
<td>39</td>
<td>.115</td>
<td>.115</td>
</tr>
<tr>
<td>Nev*</td>
<td>42</td>
<td>.115</td>
<td>.115</td>
</tr>
</tbody>
</table>

* Patients with Thromboangiitis Obliterans

the clearance constant. The injection of Priscoline was not considered intra-arterial unless the following were present; a pulsatile red column seen in the syringe, obvious and intense flushing of the skin, evidence of a pilomotor response of the skin of the limb, and the sensation of heat extending down the extremity. The radiosodium injection was made two to three minutes after completion of the intra-arterial injection.

The apparatus described by Mufson was used for the intra-arterial infusion of Priscoline. Priscoline, previously demonstrated, a curve consisting of two components was obtained when radiosodium clearance from muscle was observed for one hour. Background activity, due largely to sodium deposited in subcutaneous tissue, was derived from a straight line drawn through the last 8 to 10 plotted points on the curve and extrapolated back. This background activity was then serially subtracted from the raw data. The clearance from muscle was finally calculated from the slope of the straight line obtained by plotting the net activity.
In the studies on radiosodium clearance from skin, a straight line slope was obtained from a semi-logarithmic plot of the raw data. The time taken for the activity present initially to be decreased to one-half is the clearance half life. The clearance constant (K) is equal to the natural logarithm of two divided by the clearance half life; thus \[ K = \frac{\log_2}{T_{\frac{1}{2}}} \].

Results

The results for each experiment are expressed both in terms of clearance half life and clearance constant.

There were 49 studies of the clearance of radiosodium from the gastrocnemius muscle in 12 patients with arteriosclerosis obliterans; of these 27 were controls; the remaining 22 were studies of clearance from muscle of a rapid injection of 37.5 mg. of Priscoline into the femoral artery. The average clearance constant for the 12 patients with arteriosclerosis obliterans was 0.075 minute⁻¹. The average clearance constant for these same 12 patients following the injection of Priscoline

intra-arterially was 0.083 minute⁻¹. These results are shown in Table 2.

In two patients with thromboangiitis obliterans, the rapid injection of Priscoline into the femoral artery did not produce any significant change in the clearance of radiosodium from the gastrocnemius muscle when compared with control studies (Table 2).

Table 3 gives the results of 15 observations on the clearance of radiosodium from the gastrocnemius muscle in six individuals with normal cardiovascular systems. Six of these studies were performed immediately following the rapid intra-arterial injection of 37.5 mg. of Priscoline, and nine were control studies.

The average clearance constant for the six subjects studied was 0.113 minute⁻¹, while the average clearance constant following injection of Priscoline was 0.126 minute⁻¹.

Table 4 gives the results of 14 observations on the clearance of radiosodium from the skin over the calf of five patients with arteriosclerosis obliterans. There were seven control studies and seven studies immediately after the rapid injection of 37.5 mg. of Priscoline.
into the femoral artery of the same limb. The average clearance from the skin in these subjects was 0.035 minute\(^{-1}\), while in these same subjects the average clearance constant following the injection of Priscoline was 0.059 minute\(^{-1}\), an increase of 69 per cent in the average clearance constants. In all patients studied, there was a marked increase in clearance of radiosodium from skin after the intra-arterial injection of Priscoline. This increase ranged from 42 to 119 per cent. In one patient, G. H., in whom Priscoline was inadvertently injected into the femoral vein, no increase in clearance from the skin was noted.

**Discussion**

A vasodilator drug given orally or intravenously will result in a generalized vasodilation which will not give an increased flow of blood to a local area, assuming no change in cardiac output. In arterial peripheral vascular disease there is organic narrowing of the lumen of involved vessels. Such vessels will offer greater resistance to the dilatation effect of drugs than the uninvolved vessels of the body. Therefore, any drug producing a generalized vasodilatation would be an ineffective method of producing an increased blood flow in diseased peripheral vessels. In order to get a localized vasodilatation and to minimize any possible effect on cardiac output in our studies, the drug was given by injection into the femoral artery.

Priscoline (benzylimidazoline), now widely used as a vasodilator in peripheral vascular disease, was the drug selected for study. The complex pharmacodynamic relationships in animals caused by this drug have been described by Ahlquist and co-workers.\(^{11}\) They observed peripheral vasodilatation, cardiac stimulation, coronary vasodilatation and an increased cardiac output. However, Grimson\(^{12}\) found no significant changes in cardiac output following the intravenous injection of Priscoline, as determined by cardiac catheterization and variable results, using the ballistocardiograph. Chess and Yonkman\(^{14}\) studied the effect of Priscoline in animals and stressed the varying sympatholytic and adrenolytic properties of the drug.

It is evident from the clinical chart (table 1) that all the subjects not considered normal in this study had definite occlusive peripheral vascular disease with findings of absent pulses and decreased to absent oscillometric readings in the involved areas. In only two of the 12 patients with arteriosclerosis obliterans was there evidence of vasospasm suggested by a good response to either posterior tibial block or the Landis-Gibbon test.

In normal subjects the average response to intra-arterial injection of Priscoline was small (7 per cent). The average control clearance constant was \(0.113 \pm 0.012\) minutes\(^{-1}\) compared with the average \((K)\) following Priscoline injection of \(0.126 \pm 0.015\) minutes\(^{-1}\).\(^*\) The effect of Priscoline is small but statistically significant.

If the same statistical analysis is applied to the results for patients with arteriosclerosis obliterans, the increase following Priscoline is 15 per cent and the range for the average clearance constant of the control studies will be \(0.075 \pm 0.004\) minutes\(^{-1}\). The average \(K\) for these patients following Priscoline injection was \(0.083 \pm 0.008\) minutes\(^{-1}\), again indicating that the effect in muscle was statistically significant although too small to be clinically important.

In the skin of the patients with arteriosclerosis obliterans, the response to Priscoline was much more marked. There is an average increase of 69 per cent if the means for the control clearance constant and the clearance constant following Priscoline injection are compared. The increases varied in each individual from 42 to 119 per cent. If the same statistical analysis as above is applied here the range for controls will be \(0.036 \pm 0.012\) minutes\(^{-1}\), while the mean clearance constant following Priscoline is \(0.0588 \pm 0.0218\), showing a much greater response of the blood vessels in the skin than the blood vessels in the muscle.

In two of our subjects who had evidence of vasospasm and in two patients with minimal

\* The standard error is found from the formula:

\[
\text{Standard Error} = \sqrt{\frac{\text{Sum of Differences from mean}^2}{\text{Number of studies}}}
\]
occlusive changes the response to intra-arterial Priscoline was in no way strikingly different from the other patients in this group.

The average clearance constant of the 12 patients with arteriosclerosis obliterans in this study was 0.075 minutes⁻¹; the average clearance constant for the normals studied was 0.111 minutes⁻¹, and the average clearance for the patients with thromboangiitis obliterans was 0.116. If these figures are compared with the average clearance constant for the muscle of 101 normal subjects of 0.106 minutes⁻¹, as reported by Wisham and Yalow, it becomes evident that the clearance rate in patients with arteriosclerosis obliterans is considerably slower than in normals, as expected, that in the present series the mean clearance constant in the normal subjects agrees very closely with that previously obtained (slightly more than a 5 per cent difference), and that the clearance constants for patients with early thromboangiitis obliterans are very similar to those of normals.

Cooper and co-workers noted a more rapid clearance of radiosodium from the gastrocnemius muscle in patients in the early stages of thromboangiitis obliterans than in normal patients. We have noted a similar tendency in the two cases herein reported and in two additional unpublished cases. However this increased rate of clearance is small and is not statistically significant.

An extensive study of peripheral blood flow by various methods was reported by Cooper and Elkin. One method was the local clearance of radiosodium from the muscle. They reported that the clearance rate of radiosodium from the muscle was slowed when Priscoline was given intravenously. They concluded that the increase in blood flow to the skin caused a diversion of blood from muscle, thus resulting in a smaller blood flow to muscle. This disagrees with our finding of a small increase in the muscle clearance rate. In their study the clearance rate was determined for 10 minutes as a control and then Priscoline was given intravenously, as compared with the intra-arterial injection in our experiments, and the clearance rate again determined. It has previously been observed that a consider-

able amount of the injected radiosodium is cleared shortly after injection into a muscle and that some of the radiosodium is deposited in subcutaneous tissue. The recorded activity from subcutaneous tissue, where the clearance rate is considerably slower, then becomes a significant factor. This may well account for the discrepancy between their results and ours.

![Figure 1](image1.png)

**Fig. 1.** A scattergram showing the clearance constants in normal and pathologic muscle and skin.

![Figure 2](image2.png)

**Fig. 2.** A comparison of the response to rapid intra-arterial injection of Priscoline in normal and arteriosclerotic muscle and skin.

However our conclusions are in agreement: the major vasodilator effect of Priscoline is on the skin.

Murphy and associates studied the effect of Priscoline given intravenously on peripheral blood, using both the venous occlusion plethysmograph and the radiosodium clearance methods. They reported an average increase of 59 per cent in blood flow as determined by the plethysmograph and a decrease of 36 per cent
in muscle blood flow with the clearance technic. These investigators used the method described by Cooper and Elkin,\(^3\) which has been discussed above. They suggested that the decrease in muscle blood flow was probably a result of the increased blood flow in the skin. That such a mechanism does not take place is indicated by our finding of a small increase in muscle blood flow; although we agree with these investigators that the major effect of Priscoline is on the blood vessels of the skin.

The increase in over-all blood flow of 59 per cent following injection of Priscoline intravenously is not inconsistent with our findings of an average increase of 69 per cent in skin and an average increase of 11 per cent in muscle following injection of Priscoline intra-arterially.

The authors feel that the radiosodium clearance method is a valuable tool in obtaining information on the effect of a therapeutic agent on the various tissues of an extremity in health and disease. Since the effect of Priscoline on local muscle flow is small and far less than the effect of moderate exercise,\(^7\) the value of this drug in relieving intermittent claudication in patients with organic occlusion is questionable. Its suggested use for maintaining the integrity of the skin in peripheral vascular disease appears to have some justification when the drug is administered intra-arterially.

**Summary**

1. The effect of Priscoline administered by rapid injection intra-arterially on the clearance of radiosodium from the gastrocnemius muscle and overlying skin was studied in patients with peripheral vascular disease and in normal subjects.

2. In 59 studies on 12 patients with arteriosclerosis obliterans and two patients with thromboangiitis obliterans, and 15 studies on six normal subjects, Priscoline caused a small but not clinically important increase in the clearance rate of radiosodium from gastrocnemius muscle.

3. There was a significant increase (average of 69 per cent) in radiosodium clearance from the skin overlying the calf muscle in 14 experiments on five patients with arteriosclerosis following the intra-arterial injection of Priscoline.

4. The possible clinical implications of these observations have been discussed.

**Sumario Espanol**

El efecto de la Prisolina administrada intrarterialmente en la circulación sanguínea efectiva del músculo y la piel en sujetos normales y pacientes perifero vasculares se determinó mediante la técnica de la eliminación del radiosodio. El único incremento de significado clínico en el promedio de eliminación de Na\(^{24}\) ocurrió en la piel; el promedio de eliminación en el músculo mostró solamente ligeros incrementos que fueron constantes pero no considerados como clínicamente significantes.

**References**


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