The Circulatory Effects of Roniacol
A Physiologic Study in Normal Man

By G. S. Roback, M.D., M.S., and A. C. Ivy, Ph.D., M.D.

The vasodilatory effects of nicotinic alcohol tartrate (Roniacol) were tested on 12 normal adult males, utilizing digital venous occlusion plethysmography, brachial and digital artery oscillometry and flicker photometry. Orally administered Roniacol in single doses up to 200 mg. has no significant effect on the auscultatory blood pressure, pulse rate, or peripheral arterial circulation of normal individuals.

THERE ARE numerous pathologic conditions having as a common factor arterial insufficiency. These are mainly due to partial or complete reduction in arterial or arteriolar luminal size. This decrease is usually due to organic changes in the vessels, abnormal increase in the sympathetic vascular tone, or a combination of the two.

Various methods have been used in an attempt to increase the arterial blood supply. Locally acting agents and agents that act by the decrease of sympathetic vascular tone have been tried in an attempt to increase the functional vessel size or to increase the collateral circulation by maximal vasodilatation.

Temporary subjective improvement of peripheral arterial insufficiency has frequently been associated with the use of a new drug or type of treatment. The typical clinical course, however, is improvement for only a short period of time; either the basic pathologic processes progress, or the psychologic amelioration disappears, and the patient returns to the former status, or is frequently worse.

In order to determine objectively the effects of various drugs or treatments on the changes in peripheral arterial circulation in the human, various methods have been used. The most common have been: (1) variations in skin temperature, (2) exercise tolerance, (3) venous occlusion plethysmography, and (4) oscillometric volume fluctuations of the major or smaller vessels.

Skin temperature changes, being a measure of the skin circulation only, give only a suggested interpretation of the actual circulation in the deeper structures. Normal ranges of skin temperature have been demonstrated in individuals with markedly impaired muscular circulation.1

Exercise tolerance, although frequently an excellent index of muscular anoxia in the lower extremities, is too greatly related to the psychologic situation to serve as more than a clinical test for individual responses. It can not be considered reliable for the purpose of investigation of the physiologic effects of vasodilator drugs or new types of treatment unless continued over long periods of time. Many initial reports of effective vasodilator drugs have proved disappointing after prolonged trial where too much significance has been placed on the initial subjective improvements.

Venous occlusion plethysmography1, 2 and oscillometry2 have proved to be reliable means of measuring peripheral circulatory changes.

The flicker fusion threshold has been previously shown to be a reliable and sensitive indicator of the depressing action of anoxia and to reflect the generalized vascular response to vasodilators by alteration in the flicker fusion threshold. In the normal individual, vasodilation has been shown to produce a depression of the flicker fusion threshold by congestion and relative anoxia of the visual apparatus. In the vasospastic individual there is an increase of the flicker fusion threshold by removing the spasm and thus increasing the blood supply.4

Digital venous occlusion plethysmography, brachial and digital artery oscillometry, and flicker photometry were utilized in this study.

From the Department of Clinical Science, University of Illinois College of Medicine, Chicago, Ill.
PURPOSE

The purpose of this investigation has been to evaluate the vasodilatory effects of Roniacol* (nicotinic alcohol tartrate). Numerous clinical evaluations of this drug have been made, with rather consistently favorable vasodilatory results reported.5-7 Roniacol has been reported as having a vasodilatory effect on both coronary and peripheral circulation.8

However, clinical evaluation has been made on a purely subjective level without measurement of changes in actual circulatory volume.

CHEMICAL PROPERTIES OF RONIACOL

Roniacol is a 3-pyridine-methanol or β-pyridyl-carbinol (the alcohol corresponding to nicotinic acid) with the following structural formula:

\[
\begin{align*}
\text{H} & \quad \text{C} \\
\text{HC} & \quad \text{C—CH}_2—\text{OH} \\
\text{HC} & \quad \text{CH} \\
\end{align*}
\]

It is a nonvolatile colorless liquid with a slight characteristic odor and is freely soluble in water and alcohol. Aqueous solutions are practically neutral.9

PROCEDURE

MATERIALS. All oscilometric and venous occlusion plethysmographic determinations were made with the Johnson Recording Oscilometer,10 a simple apparatus recording the peripheral volume pulse wave on photographic paper. It consists of a reinforced blood pressure cuff that is applied around the appendage to be measured. The greatest systolic amplitude of the peripheral volume wave is determined from tracings taken at each 5 mm. Hg occlusion pressure level from 20 mm. above auscultatory systolic pressure to 20 mm. below auscultatory diastolic pressure. Changes in the volume pulse wave are transmitted to the recording system through a damped metallic diaphragm. The recording system is attached to a calibrated pipet in which a small droplet of 95 per cent ethyl alcohol moves freely with changes in displaced air volume. The movement of the alcohol droplet is recorded by focusing a beam of light on moving photographic paper in a camera container.

The recording apparatus is used to measure absolute blood inflow volume in the finger by replacing the blood pressure cuff and diaphragm with a glass cylinder placed on the finger and sealed proximally with a rubber diaphragm, while the opposite end is attached by means of rubber tubing directly with the measuring pipet containing the alcohol droplet. Sudden venous occlusion at 60 mm. Hg pressure on the wrist converts the apparatus into a venous occlusion plethysmograph.

The flicker fusion thresholds were determined with the Krasno-Ivy Flicker Photometer.5 Control levels of the flicker fusion threshold were obtained by seating the subject 5 feet from the flicker photometer in an evenly lighted room and while the subject concentrated on the flicker photometer light, reducing the flickering light from about 2900 flashes per minute until the subject reported “flicker.” The procedure is repeated until approximately the same rate occurs three times consecutively. The same procedure is used after the administration of the test drugs.

METHODS. Twelve normal white men, varying in age from 20 to 60 years, were used in all tests. For each determination the individuals were rested for 30 minutes before the control readings were taken. Room temperatures varied between 20 and 23 C. All the determinations were made with the subjects in the sitting position.

Each individual was tested twice with the placebos of lactose, and with 50, 100, and 200 mg. of Roniacol. Each test was done on a different day, but only twice weekly to prevent adaptation to the drug. The drugs were prepared in identical tablets and taken orally. Oscilometric tracings from the right arm, pulse rates, and auscultatory blood pressures, were taken from each individual as controls, and repeated every 30 minutes for three hours after oral administration of the tablets.

The tests were repeated with identical drugs and doses, each again on different days, twice weekly. Oscilometric tracings were taken from the third finger right hand. Simultaneous flicker fusion thresholds were determined. Determinations of both were taken before the drugs were administered, and every 30 minutes thereafter for three hours.

The procedure was again repeated with the identical drugs and doses. Digital venous occlusion plethysmographic volume changes were recorded utilizing the Johnson Recording Oscilometer.

RESULTS

GENERAL EFFECTS OF RONIACOL

The symptomatic effects of Roniacol taken orally in the postabsorptive state are similar to those previously reported.8 In this study the typical response began in anywhere from 5 to 30 minutes, although usually in 10 to 15

---

* Roniacol is a registered trademark of Hoffmann-La Roche, Inc., Nutley, New Jersey, and the material was kindly furnished by them.
minutes, and lasted from 10 to 60 minutes. The onset usually began with a warm, prickling or tingling sensation, starting on the face and spreading to the forehead, ears, back of the neck, upper chest (especially anteriorly), usually progressing to the forearms and hands, occasionally to the legs and feet and rarely to the torso. Occasionally these sensations became burning and extremely unpleasant. A visible flush usually followed the onset of the

Circulatory Effects of Roniacol

Results of all tests are summarized in table 1, and all statistical comparisons of significance in table 2.

(a) Brachial Arterial Oscillometry. After oral administration of 50, 100, and 200 mg of Roniacol, there were no significant changes of the average blood flows for the test period of three hours when compared with the pre-Roniacol blood flow control values (p > 0.5),

Table 1.—Circulatory Effects of Roniacol*  
For three-hour test period

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Roniacol 50 mg.</th>
<th>Roniacol 100 mg.</th>
<th>Roniacol 200 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Rate of Brachial Blood Flow†</td>
<td>1937.2 ± 93.2</td>
<td>1925.7 ± 84.3</td>
<td>1978.9 ± 74.2</td>
<td>1962.4 ± 64.0</td>
</tr>
<tr>
<td>Maximal Change of Brachial Blood Flow†</td>
<td>+250.1 ± 108.2</td>
<td>+142.6 ± 154.9</td>
<td>-15.2 ± 167.3</td>
<td>-24.9 ± 170.0</td>
</tr>
<tr>
<td>Average Rate of Digital Blood Flow†</td>
<td>200.2 ± 20.2</td>
<td>202.6 ± 17.7</td>
<td>189.7 ± 15.7</td>
<td>194.9 ± 25.9</td>
</tr>
<tr>
<td>Maximal Change of Digital Blood Flow†</td>
<td>-29.8 ± 29.7</td>
<td>-49.5 ± 29.3</td>
<td>+17.1 ± 23.3</td>
<td>-49.5 ± 36.6</td>
</tr>
<tr>
<td>Average Pulse Rate Per Minute</td>
<td>61.6 ± 2.4</td>
<td>60.4 ± 2.7</td>
<td>58.6 ± 2.4</td>
<td>61.2 ± 2.6</td>
</tr>
<tr>
<td>Maximal Change in Pulse Rate Per Minute</td>
<td>1.9 ± 3.0</td>
<td>0.8 ± 2.7</td>
<td>0.5 ± 2.9</td>
<td>4.2 ± 3.1</td>
</tr>
<tr>
<td>Average Systolic Pressure in mm. Hg</td>
<td>115.8 ± 9.5</td>
<td>115.1 ± 11.7</td>
<td>110.1 ± 8.0</td>
<td>113.7 ± 7.1</td>
</tr>
<tr>
<td>Average Diastolic Pressure in mm. Hg</td>
<td>69.6 ± 7.0</td>
<td>67.3 ± 7.6</td>
<td>66.0 ± 6.0</td>
<td>66.5 ± 7.2</td>
</tr>
<tr>
<td>Average Maximal Change in Systolic Pressure</td>
<td>-1.1 ± 1.8</td>
<td>-0.7 ± 1.8</td>
<td>1.5 ± 1.4</td>
<td>0.9 ± 1.2</td>
</tr>
<tr>
<td>Average Maximal Change in Diastolic Pressure</td>
<td>0.9 ± 1.9</td>
<td>0.9 ± 0.7</td>
<td>1.5 ± 1.6</td>
<td>1.3 ± 1.8</td>
</tr>
<tr>
<td>Average Digital Blood Flow by Venous Occlusion Plethysmography</td>
<td>3.6 ± 1.3</td>
<td>3.5 ± 1.6</td>
<td>3.7 ± 1.6</td>
<td>3.4 ± 1.8</td>
</tr>
<tr>
<td>Maximal Flicker Fusion Threshold Change</td>
<td>29.0 ± 11.4</td>
<td>26.7 ± 16.5</td>
<td>30.0 ± 33.2</td>
<td>28.3 ± 25.6</td>
</tr>
</tbody>
</table>

* All values represent averages of 12 normal male subjects.
† Measured in oscillometric units.

symptomatic effects, but occasionally preceded or occurred simultaneously. The pattern of the flush was usually similar to the paresthesia. The flush usually lasted longer than the paresthesia.

Slight stomach ache, nausea, and headache occurred rarely. The extent of both the symptomatic effects and the visible flush were directly related to the dosage, usually none being present with 50 mg Roniacol and almost always and to greater degrees with 200 mg Roniacol.
(p > 0.5). The average systolic and diastolic blood pressures for the 12 subjects showed only slight average variation (fig. 2).

There was no significant difference between the normal physiologic variations in pulse rate with placebo and the pulse rates after oral administration of 50, 100, and 200 mg. Roniacol (p > 0.5). The average pulse rates for the 12 subjects showed very small average variations during the three hours (fig. 3). The average maximal pulse rate change from the pre-Roniacol levels was 0.75 ± 2.7 beats per minute after 50 mg. Roniacol, 0.5 ± 2.9 beats per minute after 100 mg. Roniacol, and 4.2 ± 3.1 beats per minute after 200 mg. Roniacol, compared with the 1.9 ± 3.0 beats per minute after the placebo.

(b) Digital Oscillometry. Average blood flow

Table 2.—Statistical Significance of Comparison of Blood Flow Changes between Placebo and Various Doses of Roniacol

<table>
<thead>
<tr>
<th>Comparison between Placebo and Roniacol Dose</th>
<th>No. Subj.</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital arterial blood flow (maximal changes)</td>
<td>50 mg.</td>
<td>12</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>0.43</td>
</tr>
<tr>
<td>Digital arterial blood flow (average three-hour flow)</td>
<td>50 mg.</td>
<td>12</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>0.26</td>
</tr>
<tr>
<td>Maximal change in pulse rate</td>
<td>50 mg.</td>
<td>12</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic blood pressure changes</td>
<td>50 mg.</td>
<td>12</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>0.62</td>
</tr>
<tr>
<td>Diastolic blood pressure changes</td>
<td>50 mg.</td>
<td>12</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>0.64</td>
</tr>
<tr>
<td>Brachial arterial blood flow (maximal changes)</td>
<td>50 mg.</td>
<td>12</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>1.20</td>
</tr>
<tr>
<td>Brachial arterial blood flow (average 3 hour flow)</td>
<td>50 mg.</td>
<td>12</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>0.22</td>
</tr>
<tr>
<td>Digital venous occlusion plethysmographic blood flow changes</td>
<td>50 mg.</td>
<td>12</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>0.94</td>
</tr>
<tr>
<td>Flicker fusion threshold changes</td>
<td>50 mg.</td>
<td>12</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>100 mg.</td>
<td>12</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>200 mg.</td>
<td>12</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Fig. 1. Effects of Roniacol on brachial arterial blood flow. In all figures, individual points on the graph represent the average of 12 normal male subjects. The vertical lines represent the standard errors of the group means.

Fig. 2. Effect of Roniacol on auscultatory systolic and diastolic pressure. See also legend to figure 1.

Fig. 3. Effects of Roniacol on pulse rate. See also legend to figure 1.

values for the three-hour test period for the 12 subjects, in amplitude oscillometric units per minute, show no statistically significant
difference between the physiologic variation in placebo values during the three hours and the maximal individual fluctuations of the circulatory flow after oral administration of 50, 100, and 200 mg of Roniacol \((p > 0.5)\). The average rates of digital blood flow for the three-hour test period after administration of placebo, 50, 100, and 200 mg of Roniacol are shown in figure 4.

(c) \textit{Digital Venous Occlusion Plethysmography}. There was no significant variation in the average blood flow for the three-hour duration of the test after 50, 100, and 200 mg of Roniacol when compared with the placebo values or the pre-Roniacol blood flow levels \((p > 0.5)\).

(d) \textit{Flicker Photometry}. There was no significant variation in the average maximal flicker fusion threshold change for the three-hour duration of the test after administration of 50, 100, and 200 mg of Roniacol, when compared to the pre-Roniacol control values or the placebo values \((p > 0.5)\).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{roniacol_effects_graph.png}
\caption{Effects of Roniacol on digital blood flow. See also legend to figure 1.}
\end{figure}

\textbf{DISCUSSION}

The rate of blood flow in the hand and foot is changed readily by vasoconstrictor stimuli, although the circulation in the forearm and leg is, for the most part, unaffected by stimuli which do not have a cardiovascular effect and enhanced by those which appear to increase cardiac output.\(^{12}\) As Roniacol produces no significant change in blood pressure, pulse rate or the systolic ejection expansion of the brachial artery, it consequently appears to have no significant effect on cardiac output.

Roniacol has no significant effect on digital blood flow as measured both in oscillometric units, and directly by venous occlusion plethysmography.

As the volume pulse is a sensitive indicator of the vasomotor activity which is of insufficient degree to show itself on blood pressure changes,\(^1\) lack of significant alteration of the volume pulse following oral administration of 50, 100, and 200 mg of Roniacol indicates that it has no significant effect on the sympathetic vasomotor tone in the upper extremity. As the lower extremity normally has even a higher degree of sympathetic tone than the upper extremity\(^1\) even less effect would be expected on the lower extremity.

The lack of significant change of the flicker fusion threshold indicates that Roniacol has no significant vascular effects on the visual apparatus. With vasodilation there would have been marked depression of the threshold.

It is unlikely that any significant transient effects occurred between determinations, as most of the 30-minute determinations were made during the period of both maximal symptoms and visual flush.

The presence of flush without measurable changes in circulation, as determined by the tests employed in this study, probably indicates that the clinical effects of Roniacol are due to dilatation of the skin capillaries. This might account for some of the favorable results reported with chronic trench foot\(^6\) and with gangrenous skin.\(^7\) The failure to demonstrate circulatory changes despite the visible flush may be due to several factors, such as (1) insufficient sensitivity of the tests for recording the effects of flushing, or (2) concomitant vasoconstriction in other vessels in the same limb, thus producing no change in the total blood flow. These studies were performed using single doses of Roniacol on normal men and do not necessarily indicate the action of the drug when given continuously in the treatment of disease.
SUMMARY AND CONCLUSIONS

Orally administered Roniacol in single doses up to 200 mg. has no significant effect on the auscultatory blood pressure, pulse rate, or circulation of normal individuals as measured by: (1) brachial arterial and digital oscillometry, (2) digital venous occlusion plethysmography, and (3) flicker photometry.

REFERENCES

9 Pharmacological properties as stated by the manufacturer, Hoffmann-La Roche, Inc., Roche Park, Nutley, New Jersey.
The Circulatory Effects of Roniacol: A Physiologic Study in Normal Man
G. S. ROBACK and A. C. IVY

Circulation. 1952;6:90-95
doi: 10.1161/01.CIR.6.1.90

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1952 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/6/1/90

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/