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Influence of Benzyl-Imidazoline on the Peripheral Circulation of Man.*

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Studies have shown that 2-benzyl-4,5-imidazoline hydrochloride (Priscol hydrochloride-Ciba) has certain properties which may be useful in augmenting the volume of blood flow to the periphery in man.[1] It reverses the hypertensive effect of epinephrine to a hypotensive one through an adrenolytic action.[2] Following the use of this drug in animals, peripheral vasodilatation cardiac stimulation, and an increased cardiac output have been shown.[2] The present study was carried out to determine the effects of the intravenous injection of this drug upon the peripheral circulation in normal individuals and patients with arteriosclerotic obliterative disease and thromboangiitis obliterans.

Methods and materials. Seventy male subjects without evidence of peripheral vascular disease, between the ages of 18 and 45 (average 26) and 10 subjects with organic obliterative disease, between the ages of 35 and 55 (average 51) were studied. Of the latter 7 had arteriosclerosis obliterans and 3 thromboangiitis obliterans. The volume change of the digits was determined using the Cambridge pneumo-plethysmograph[3] and the venous occlusion method.[4] The right or left second toe tip and right or left index finger tip were enclosed in a digital cup from which volume changes were recorded. The collecting cuff was placed at the wrist or ankle. Venous occlusion was ordinarily accomplished by quickly inflating a ribbed-type blood pressure cuff to a pressure of 60 mm of mercury. Lower pressures were often employed in patients with vascular disease. Plethysmograms were standardized so that volume changes were obtained in cu mm per 5 cc of tissue per second. The amplitude of pulsations was recorded in cu mm per 5 cc of tissue. Normal subjects were used as controls for the patients with organic disease. Also control recordings were taken before and at frequent intervals after the injection of the drug so that each subject acted as his own control. Skin temperatures were obtained from a Micromax automatic 4-point recorder which recorded from each thermocouple junction every 2 minutes. Recordings were also made using a Brown Electronik 4-point potentiometer which recorded from each junction every 30 seconds. The readings were accurate to $\pm$ 0.25°C. The accuracy of the instruments was tested using a National Bureau of Standards mercury thermometer which could be read accurately to 0.1°C. The thermocouple junctions were taped to the skin with cellulose tape and inserted into the muscle or subcutaneous tissue of the calf using a specially prepared needle. Determinations were made under standard reproducible conditions. The patients had a normal meal the night before the test. They reported, without breakfast, to the laboratory, dressed in a gown and bathrobe. They rested 45 minutes prior to the test. Their bodies were covered by their robes with no additional blankets during the test (except as described below). The determinations were made in a closed room without draughts. The room temperature did not vary more than $\pm$ 1.5°C during an experiment. Indirect heating of the subjects was produced by covering them with 2 wool blankets (the finger tips and toe tips were exposed)

* The opinions held are those of the authors and not necessarily those of the Veterans Administration.

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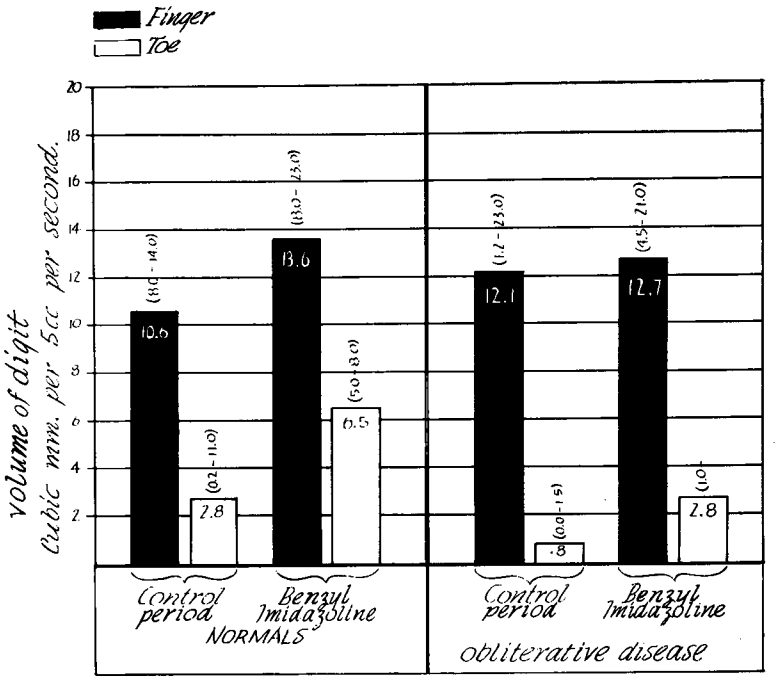

FIG. 1.

Effect of benzyl-imidazoline on the volume of the finger tip and toe tip in 10 normal individuals and 7 patients with arteriosclerotic obliterative disease and 3 patients with thromboangiitis obliterans. The average of 10 determinations was taken on each subject before and 30 minutes after benzyl-imidazoline.

and placing 1 hand and forearm in water at 45°C for 20 minutes. In all experiments 50 mg (5 cc) of benzyl-imidazoline were injected intravenously.

Effect of benzyl-imidazoline on the volume and amplitude of pulsation of the digits. Ten normal subjects and 10 patients with obliterative arterial disease (7 with arteriosclerosis and 3 with thromboangiitis obliterans) were studied (Fig. 1). The room temperature averaged 24°C. In the normal group benzyl-imidazoline increased the volume of the toe tip 1.3 times over that of the control. In the finger tip in this group the change was from 10.6 to 13.6. In patients with obliterative disease the volume of the toe tip increased 2.5 times over that of the control. In the finger tip in this group the change was from 12.1 to 12.7.

Benzyl-imidazoline produced no appreciable change in amplitude of pulsation in the toe tip and finger tip, the values averaging 0.4 before and 0.5 cu mm per 5 cc 30 minutes after in the former and 1.5 and 0.8 cu mm per 5 cc in the latter.

Effect of benzyl-imidazoline on temperatures of deep and superficial tissues. Serial body temperatures were recorded from several body regions before and after injection of benzyl-imidazoline. Ten normal subjects were allowed to rest for 40 to 60 minutes until temperatures varied no more than 0.5°C before the drug was administered. Thirty minutes after injection the temperatures (degrees Centigrade) increased over the resting temperature as follows: forehead 1.0, index finger 1.0, muscle of the calf 0.5, subcutaneous tissue of the calf 0.25, skin of the calf 0.5, skin of the toe 3.75. There was no measurable alteration in the rectal temperature. Thus, benzyl-imidazoline was most effective in increasing the skin flow of blood of the toe.

Effect of indirect heating after benzyl-imidazoline on temperatures of the lower extremity. In 10 normal subjects, at a room temperature which averaged 25°C, benzyl-

imidazoline produced a definite increase in skin temperature which was greatest on the large toe (from 29.5°C to 33.25°C in 56 minutes). The increase in temperature of the skin of the calf, subcutaneous and intramuscular tissue of the calf was less. Indirect heating, after benzyl-imidazoline, produced a further increase in the temperatures, the change being greatest in the large toe. After immersing the arm in water 45°C, the temperature of the large toe rose to 34.4°C. Thus, indirect heating of one arm following benzyl-imidazoline augmented the skin flow to the lower extremity.

Effect of benzyl-imidazoline on skin temperatures following indirect heating. Ten normal subjects were studied. The room temperature averaged 24°C. After 20 minutes of indirect heating the average skin temperature of the dorsum of the left foot was 34.6°C, indicating maximum skin temperature effect ordinarily produced by this procedure. Thirty-two minutes after benzyl-imidazoline the temperature of the foot was 34.7°C. Thus, benzyl-imidazoline after indirect heating had no significant effect on the skin flow to the dorsum of the foot.

The duration of toe temperature changes following benzyl-imidazoline was determined in 10 normal subjects whose resting skin temperatures were less than 32°C. The average increase in temperature was 1.5°C in the first 8 minutes and maximum increase 3°C with a beginning decrease 50 minutes after injection.

Discussion. Benzyl-imidazoline intravenously was effective in increasing the volume of the digits and elevating the skin temperature of the lower extremities in normal individuals and in patients with arterial obliterative disease. The volume changes produced by benzyl-imidazoline were only ¼ as large as the volume changes produced by indirect body heating or arterial occlusion for 5 minutes. It is possible that the intra-arterial injection of this drug would be more effective if tissue fixation is high. The greatest increase in temperature was recorded from the skin of the toe. This effect on skin temperatures occurred within 8 minutes after intravenous injection and after approximately 50 minutes a beginning diminution in effect was noted. A greater increase in temperature and blood flow would probably have been recorded if subjects had been in a state of vasoconstriction prior to the administration of benzyl-imidazoline. The more superficial tissues of the lower extremities showed the greatest elevation in temperature. The temperatures of the rectum, forehead, finger, muscles and subcutaneous tissues of the calf changed relatively little. Benzyl-imidazoline was not effective in raising the skin temperature of the extremities after vasodilatation had been produced by indirect heating. Certain patients with arteriosclerotic obliterative disease responded to the drug with an increased skin flow to the periphery.

In these experiments toxic effects were few. The drug was administered very slowly and was discontinued if signs of toxicity were noted. On two occasions benzyl-imidazoline shock developed with a decrease in rate of blood flow to the periphery, with pallor, sweating and weakness.

The increase in rate of blood flow to the lower extremities is probably brought about by more than one mechanism. Peripheral vasodilatation and cardiac stimulation in animals have been shown.[2] In some of its actions, benzyl-imidazoline resembles epinephrine; in others, histamine or acetylcholine; and still others, ergotamine. Vasodilatation was not prevented by atropine or by sympathomimetic agents and therefore probably was not due to acetylcholine-like or histamine-like action. The sympatholytic action is shown by the effective blocking of the pressor action of epinephrine in experimental animals. Epinephrine following benzyl-imidazoline is an active vasodilator (sympathomimetic antipressor action).[4] Benzyl-imidazoline does not prevent the cardiac stimulation produced by epinephrine. Thus, the increased flow in man may be due to peripheral vasodilatation combined with an increased cardiac output.

Summary. Benzyl-imidazoline given intravenously effectively increased the rate of blood flow to the periphery in normal individuals and in certain patients with arteriosclerotic obliterative disease. The volume change of the digits following venous occlusion and the skin temperatures were aug-

mented to a greater degree in the lower extremities than in the upper. The amplitude of pulsation showed less change than did the skin temperature or volume changes of the digits.

The greatest rise in temperature was seen in the toes. The temperature of the skin of the calf, subcutaneous tissues, and deep muscle of the calf showed a decreasing temperature effect in the order shown. The rectal temperature and temperature of the forehead showed the least change.

Benzyl-imidazoline was not effective in raising the skin temperature of the foot, forehead, or hand after indirect heating of one arm.

Benzyl-imidazoline shock was seen on 2 occasions.

The action of benzyl-imidazoline is complex, and the increased flow to the extremities may result from a combination of effects including peripheral vasodilatation, and, possibly, cardiac stimulation.

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Differential Sheep Cell Agglutination Test in Rheumatoid Arthritis.*

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One of the greatest obstacles to the objective study and evaluation of therapy in rheumatoid arthritis has been the lack of a simple and reliable laboratory test for the measurement of rheumatoid activity. Many tests have[1] been proposed in the past and several have proven useful adjuncts to diagnosis and evaluation of a patient but no one test alone is sufficiently significant to serve as sole guide for therapy. Recently Rose, Ragan *et al.*[2,3] have proposed a new simple test for activity in rheumatoid arthritis and have claimed for it a high degree of specificity and reliability. These authors discovered that the serum of patients with rheumatoid arthritis in the active stage contains a substance which agglutinates sheep erythrocytes sensitized with specific amboceptor to much higher titer than normal sheep cells. The test consists in a comparison of the titers to which normal and sensitized sheep cells are agglutinated by patients' serum. The results are expressed as "Differential titer" *i.e.* the algebraic difference between the agglutination titers observed with normal (NS) and sensitized sheep erythrocytes (SS). In patients with active rheumatoid arthritis this differential agglutination titer was found by Rose *et al.* to be "never lower than 16 and usually considerably higher." In other diseases examined (with exception of one case of ankylosing spondylitis) the differential titer was 16 or less.

In order to accumulate data on the validity and possible limitations of this laboratory test, sera from a number of patients were examined in this laboratory. The present paper reports the results from 160 patients living in Northern California, about half of whom had rheumatoid arthritis.

Materials and Methods. The technique described by Rose *et al.*[2] for the differential sheep cell agglutination test was followed in all details. Sera of patients were obtained from freshly drawn venous blood and were tested usually within 18 hours, always within 72 hours of collection. Red blood cells were obtained from a number of different sheep but all gave identical results when tested with the same sera. Special attention was paid to careful preparation of glassware to avoid any

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