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Harold W. Schnaper, Robert L. Johnson, Edward B. Tuohy, Edward D. Freis

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Research Article

THE EFFECT OF HEXAMETHONIUM AS COMPARED TO PROCAINE OR METYCAINE LUMBAR BLOCK ON THE BLOOD FLOW TO THE FOOT OF NORMAL SUBJECTS [1, 2]

By HAROLD W. SCHNAPER, ROBERT L. JOHNSON,[3] EDWARD B. TUOHY, AND EDWARD D. FREIS

(From the Cardiovascular Research Laboratory, Georgetown University Hospital, and the Departments of Medicine and Anesthesiology, Georgetown University School of Medicine, Washington, D. C.)

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In 1948, Paton and Zaimis reported on a series of polymethylene bistrimethyl ammonium compounds with unusual properties; the decamethonium (C10) member of this series exhibited marked curariform activity, while the penta- and hexamethonium (C5 and C6) compounds revealed ganglionic blocking action (1, 2). Since this report, a number of clinical studies have called attention to the favorable effects of C5 and C6 in hypertension (3–6), peptic ulcer (7) and peripheral vascular diseases (4, 8, 9). Investigations in this laboratory indicated that in a cool environment C6 produced a greater elevation of skin temperature of the digits than either tetraethylammonium salts or Priscoline (9). In addition, C6 caused less side effects and had a longer duration of action than either of the other blocking agents.

These results suggested that the increase in peripheral blood flow after administration of C6 was greater than was produced by previously known compounds and might, in fact, approach that achieved following complete blockade of the sympathetic vasoconstrictor outflow. Since the changes in skin temperature provide at best only approximate estimations of variations in peripheral blood flow, it was decided to measure quantitatively the increase of blood flow in the foot after C6, using the plethysmographic method, and to compare this increase with the presumably maximum flow obtained from regional block of the sympathetic nerves to the lower extremities.

MATERIAL AND METHODS

Blood flow was measured in the left foot using the venous occlusion plethysmograph described by Abramson (10), but with certain modifications. These changes were introduced because of the necessity of removing the foot from the plethysmograph at the time of the regional block and then replacing it rapidly to avoid delaying the determinations of blood flow. Therefore, instead of cementing the edge of a thick rubber sheeting to the ankle, a thin rubber boot was prepared, the edges of which were everted and sealed permanently to the inlet of the plethysmograph in a manner similar to that described by Krogh, Landis and Turner (11) for use with the limb segment plethysmograph. The boot was made of rubber thin and pliable enough for the pressure of the water filling the plethysmograph to press the rubber membrane snugly against the contours of the foot.[4] Since an air pocket usually formed at the upper end of the boot, the air was removed by means of small-bore plastic tubing leading from the toe of the boot to one of the two outlets of the plethysmograph. The trapped air could then be removed by applying suction to the plastic tube with a syringe. By means of this device, the foot could be sealed quickly within the plethysmograph, and valid blood flows recorded within 15 minutes after the block had been completed. The smoked drum method of recording was replaced by an electrically heated writing point attached to the Brodie's bellows and the recordings made on heat-sensitive paper.[5]

Digital pulse volume and blood flow were measured in the first toe of the opposite foot with a Burch-Winsor portable plethysmograph (12). Venous occluding cuffs for these measurements were placed at either the base of the toe or the ankle. The results of these studies will be reported in detail in another communication (13). In order to check on the completeness of sympathetic paralysis, the digital plethysmograph was used to determine sympathetic vasoconstrictor reflexes in the toe to "noxious" stimuli. The skin temperature of eight points on the body as well as air temperatures were recorded by the method previously described (9).

The 10 volunteer subjects, all healthy male medical students between 22 and 29, were lying comfortably in bed

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[3] Captain, M.C., U.S.A.F.

[4] Meteorological balloon rubber, supplied by Dewey and Almy Company, Cambridge, Mass.

[5] Permapaper, Sanborn Company, Cambridge, Mass.

with the limbs exposed throughout the procedure. They were unclothed except for shorts. The room was kept between 68 and 70 degrees by a large water-cooled air conditioner. The water in the plethysmograph was kept at a constant 32 degrees C. by means of a built-in heater and a motor-driven stirring propeller. Each subject was allowed to gain equilibrium with the room temperature for at least one hour before the first control determinations. In order to minimize the possibility of profound hypotension after the administration of C6, the foot of the bed was elevated on 2-inch blocks in all procedures.

Regional block was carried out by using lumbar epidural injection of metycaine rather than paravertebral injection of procaine because of the greater certainty of achieving complete paralysis of all sympathetic vasoconstrictor fibers to the feet. To make certain that complete paralysis had been achieved two of the subjects were later given spinal anesthesia.[6] All subjects given lumbar epidural block experienced hypesthesia of the lower extremities, and two developed anesthesia of the saddle area as well. Both volunteers subjected to intrathecal block experienced complete anesthesia to the level of the iliac crests.

In order to permit the effects of the preceding experiment to wear off completely in each subject, an interval of at least 48 hours separated the test using C6 and the procedure using regional block. The two subjects who received lumbar intrathecal block were allowed at least seven days between experiments.

Before each procedure, eight to 16 recordings of blood flow through the foot were averaged to obtain the control value. After either regional block or C6, groups of four to 10 flow measurements were recorded at various intervals up to two hours or until the skin temperature began to fall. C6 was administered intravenously as the dibromide salt. However, all dosages refer to the amount of C6 ion rather than of the salt.

RESULTS

Changes in foot blood flow

During the control period the blood flow in the foot ranged from 0.3 to 2.7 cc. per 100 cc. of foot volume per minute, with an average of 1.0 cc. (Table I, Figure 1). In most subjects the mean blood flow in the control period varied slightly from test to test but these variations never exceeded 1 cc. per 100 cc. per minute.

Following the injection of hexamethonium, the blood flow varied between 6.2 and 13.2 cc. per 100 cc. per minute, with a mean flow of 9.8 cc. (Table I, Figure 1). Following epidural block in these subjects, the flow averaged 10.2 cc. with a range of 7.1 to 15.8 cc. After C6 the maximum blood flow in five of the subjects was slightly greater than that achieved by epidural block, and in the other five slightly less.

The rate of increase of blood flow in the foot was always much more rapid after C6 than after epidural block. Maximum blood flow occurred five to 15 minutes after the intravenous administration of C6, whereas the greatest increase in blood flow after epidural block did not become evident for 25 minutes to an hour or more (Figure 2). The rate of decrease of foot blood flow following C6 varied considerably in different subjects. One hour after injection the mean flow was 74.5% of the maximum with a range of 45% to 98%. Following epidural block the rate of decrease of foot blood flow appeared to be more gradual than after C6, although, because of the delay in attaining maximum levels, the studies were not continued for a sufficient time to obtain quantitative data in all cases. Of the six cases who following epidural block attained maximum flow in less than 45 minutes, the mean flow 60 minutes after block was 76.3% of the maximum with a range of 28% to 98%.

In two subjects (J. L. and P. S., Table I), the initial experiments indicated that the increased flow of blood following 50 mg. of C6 was considerably less than that after epidural block. Because of this discrepancy, determinations of blood flow were repeated in these two subjects, using larger doses of hexamethonium. Following a dose of 75 mg. of C6 in subject J. L., the flow rose to 13.2 cc. per 100 cc. of foot volume, as compared to 8.2 cc. after the 50 mg. dose. In subject P. S. blood flow increased to 7.1 cc. after 100 mg. of C6 as compared to 5.3 cc. after 50 mg. of the drug. Thus, in both these subjects doses of C6 larger than 50 mg. were required to produce elevations of blood flow approaching the maximum.

In addition to the studies after C6 as compared to epidural block, two of the volunteers were subjected also to intrathecal anesthesia (cases L. I. and V. T., Table I and Figure 1). In subject V. T., blood flow rose to slightly higher levels after intrathecal anesthesia (9.8 cc. per 100 cc. of foot) than after either C6 (8.3 cc.) or epidural block (7.5 cc.). In subject L. I., however, the reverse occurred; the maximum blood flow was only 6.2 cc. after intrathecal anesthesia as compared to 8.7 cc. after epidural block and 10.0 cc. after C6.

[6] Metycaine 1% was used for all epidural lumbar blocks. Procaine 1% was used for all intrathecal blocks.

TABLE I

Effects of hexamethonium bromide, lumbar epidural and intrathecal anesthesia on foot blood flow in normal subjects

Subject	Age	Foot blood flow (cc. per 100 cc. of foot per minute)					
		Control	After C6 50 mg. I.V.	Control	After epidural	Control	After intrathecal
V. T.	25	1.2	8.3	0.9	7.6	0.8	9.8
L. I.	24	0.4	10.0	0.8	8.7	1.0	6.2
L. D.	28	0.3	11.6	0.6	9.1		
V. B.	25	0.9	9.2	0.6	8.8		
J. L.	22	1.2	8.2	0.7	15.8		
		1.0	13.2*				
W. B.	27	1.1	6.2	1.7	7.1		
S. O.	27	0.8	10.8	1.5	12.6		
J. D.	28	2.7	9.2	1.7	11.8		
R. B.	29	1.0	12.8	1.0	9.4		
P. S.	23	0.7	5.3	0.5	11.2		
		0.7	7.1†				

* Dosage of C6 increased to 75 mg. intravenously.
† Dosage of C6 increased to 100 mg. intravenously.

Changes in skin temperature of the toes

In every instance after either C6 or regional block with procaine, there was a marked rise of the skin temperature in the toes (Figure 3). These elevations varied between 15 and 24 degrees F. above the control values. The elevations of toe temperature were greater after epidural block than after hexamethonium in seven of the nine subjects in whom measurements were taken. In all but one (L. D.), however, the differences in skin temperature following C6 as compared to regional block were slight, amounting to less than 2 degrees F.

The changes in digital skin temperature correlated poorly with the changes in blood flow. In subjects P. S. and W. B., for example, the rise in temperature was greater after C6, yet the increase in blood flow was greater after epidural block. Similar contradictory results were obtained in three other subjects.

The rate of elevation of skin temperature proved also an unreliable index of the rapidity of increase in blood flow. Following regional block, the increase in skin temperature of the toe and foot lagged five minutes or more behind the rise in

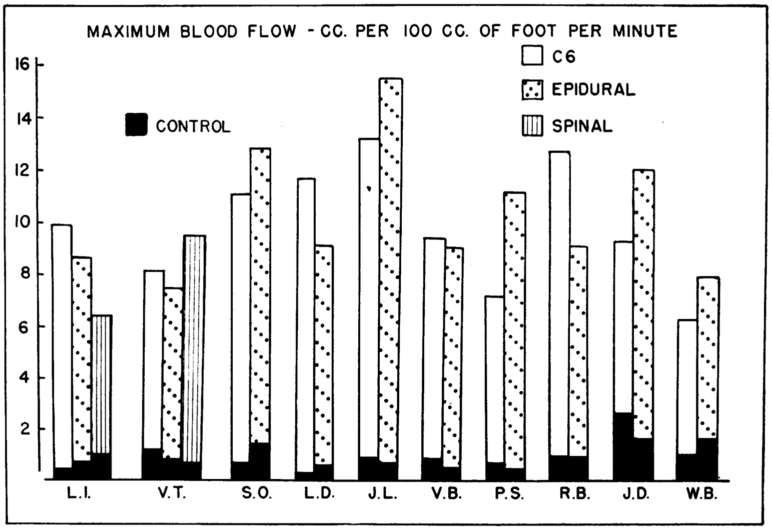

FIG. 1. CHART OF THE MAXIMUM BLOOD FLOWS IN THE LEFT FOOT FOLLOWING HEXAMETHONIUM AS COMPARED TO LUMBAR INTRATHECAL OR EPIDURAL BLOCK IN 10 NORMAL SUBJECTS

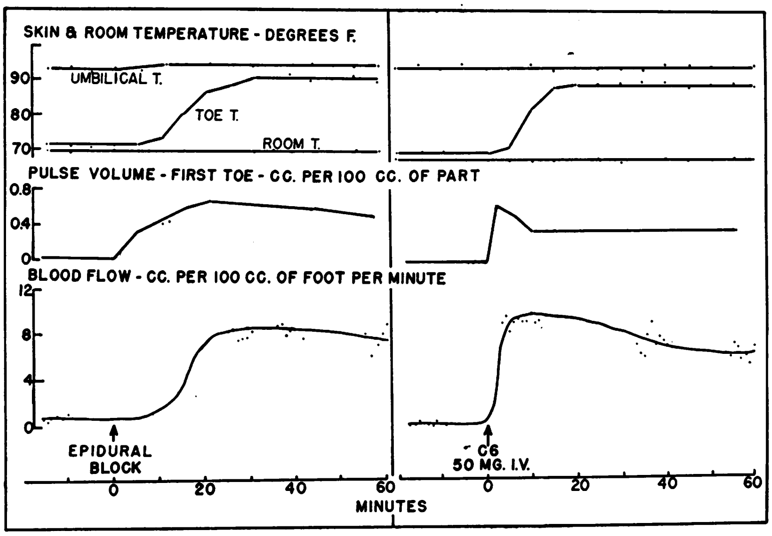

FIG. 2. CHART SHOWING CHANGES IN SKIN-TEMPERATURE, DIGITAL PULSE VOLUME AND FOOT BLOOD FLOW IN SUBJECT L. I. FOLLOWING EPIDURAL BLOCK AND FOLLOWING C6

blood flow. Furthermore, the skin temperature remained elevated for an additional 15 or 20 minutes after the plethysmographic tracings showed that the foot blood flow had passed the maximum and was decreasing.

Changes in vasoconstrictor reflexes in the toes

The changes in blood flow in the toe measured with the digital plethysmograph paralleled those in the foot. However, the digital pulse volume always exhibited a greater increase after regional block than after C6. In all instances, the sympathetic vasoconstrictor responses to "noxious" stimuli (such as a deep breath or ice applied to the forehead) were effectively blocked during the period of maximum elevations of foot blood flow following either epidural or intrathecal anesthesia or C6.

DISCUSSION

Investigations by Hoobler and his co-workers using the water-filled plethsymograph indicated that in normal subjects large doses of tetraethylammonium produced increases in foot blood flow only half as great as those obtained after lumbar paravertebral block with procaine (14). Applying heat to the trunk produced no greater increase in blood flow in the foot than did the administration of TEA, while other vasodilator drugs such as papaverine, nitroglycerine, nicotinic acid, and aminophyllin were even less effective.

In the present study the increases in foot blood flow following 50 to 100 mg. of C6 intravenously were not greatly different from those after either epidural or intrathecal block using metycaine or procaine. These results suggest that the degree of blockade of the sympathetic vasoconstrictor impulses to the feet is nearly complete after the intravenous injection of such doses of C6.

There is some evidence, however, that regional block produced a slightly greater decrease in peripheral resistance than C6. The mean of the foot blood flow values was 10.2 cc. per 100 cc. of foot volume after regional block, which was slightly greater than the mean of 9.8 cc. after C6. This difference, however, was not statistically significant. Similarly, the skin temperature elevations in the toes usually were slightly higher following regional block. In addition, it was observed that the pulse volume of the toe was consistently greater after regional anesthesia than after C6, even in those cases in which C6 produced the greater increase in foot and toe blood flows. This discrepancy, which will be discussed in detail in another communication (13), appeared to be associated with a decrease of systolic blood pressure and increase of heart rate resulting in narrowing of pulse pressure observed after C6 but not after lumbar block. In view of these various observations, it seems possible that the degree of sympathetic in-

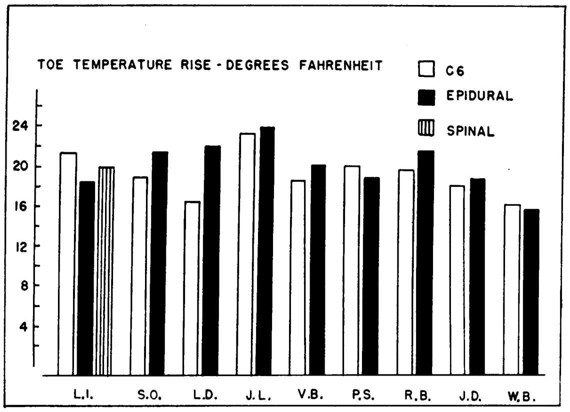

FIG. 3. CHART SHOWING THE MAXIMUM RISE OF TOE TEMPERATURE FOLLOWING C6 AS COMPARED TO EPIDURAL OR INTRATHECAL ANESTHESIA IN 10 NORMAL SUBJECTS

hibition after C6 approached but may not have achieved complete blockade in some of the subjects.

Nevertheless, these observations would appear to be at odds with the hypothesis of hemometakinesia, that is, the so-called "borrowing and lending" theory. This hypothesis states in part that the systemic administration of any vasodilating agent cannot result in as great an increase in foot blood flow as does regional block (15, 16). After regional anesthesia, blood from other portions of the body is shunted into the area of diminished resistance. However, according to this hypothesis, after systemic administration of a vasodilating agent blood cannot be diverted to any local area because the decrease in peripheral resistance is generalized.

While this hypothesis may apply to agents which act directly on the blood vessels, it is probable that the "sympatholytic" compounds act more selectively. Sympathetic vasoconstrictor nerves probably are not distributed uniformly throughout the vascular system. Actual measurement of regional blood flows after other drugs which inhibit sympathetic vasoconstrictor impulses, such as TEA (17, 18) and dihydroergocornine (19), indicates that whereas blood flow in the digits usually increases markedly, flow in the muscles and renal bed may not change significantly and hepatic-portal blood flow usually decreases. Cardiac output remains relatively unchanged (17, 19). Thus peripheral resistance in certain vascular areas such as the digits may decrease after the "sympatholytic" drugs while in other areas such as the hepatic-portal bed it may increase. Hence, as indicated by the present studies, a considerable degree of "borrowing and lending" of blood flow may occur from the action of agents which are sufficiently potent to produce complete or nearly complete blockade of sympathetic vasoconstrictor impulses.

It is apparent from the data derived from subjects J. L. and P. S. that doses of 75 to 100 mg. of C6 in some persons produce more complete ganglionic blockade than 50 mg. Hence, it would seem advisable to give 100 mg. in various clinical states when complete inhibition of sympathetic vasoconstriction is desired. In severely hypertensive, cardiac, and debilitated patients, however, profound and probably dangerous hypotension may occur after such large doses. Therefore, in actual practice, trial doses of 5 to 10 mg. have been given to these patients before increasing the dose to maximum tolerated amounts (20).

None of the subjects of the present study exhibited significant reduction of diastolic blood pressure as a result of either epidural block or hexamethonium, although there usually was a slight decrease in systolic pressure. The absence of significant hypotension in these normal, healthy young men could not be due entirely to the slightly head-down position because we have observed marked reductions of arterial pressures in hypertensive and older normotensive patients after similar doses of C6 despite this precaution (9). These results may be due to (*1*) the presence of a higher sympathetic "tone" in older as compared to younger individuals, or (*2*) to the loss of elasticity of the larger vessels in the elderly resulting in a lessened ability to counteract sudden decreases in peripheral resistance.

Because of its great potency C6 is capable of producing severe reductions of blood pressure in susceptible patients. In addition, marked postural hypotension has been a regular occurrence. During continuous administration effects secondary to parasympathetic blockade have been observed, including constipation, paralytic ileus and dry mouth. These undesirable reactions require that the drug be administered with care in patients under treatment for peripheral vascular diseases and hypertension. Methods for avoiding or circumventing such reactions in clinical cases will be described in other communications (20, 21).

SUMMARY AND CONCLUSIONS

Ten normal young male subjects in a constant, cool temperature room were subjected on alternate days either to 50 to 100 mg. of C6 ion intravenously or to lumbar extradural or intrathecal block.

1. Five of the subjects exhibited a greater increase in foot blood flow after C6 while five others had the greater flow after regional block.
2. Evidence that the sympathetic blockade produced by C6 may not have been quite complete is suggested by the fact that in the group as a whole the averages of the foot blood flow, toe blood flow and digital skin temperature changes were slightly greater after regional block than after C6. In some of the subjects, however, the values rose higher after C6 than after regional block.
3. Changes in skin temperature and digital pulse volume did not accurately reflect the changes in foot blood flow.
4. In two subjects doses of 75 and 100 mg. of C6 resulted in greater elevations of foot blood flow than doses of 50 mg.

These results suggest that C6 in doses of 50 to 100 mg. produces in man marked, and in some instances, complete blockade of the sympathetic vasoconstrictor outflow to the foot.

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