The Use of Hexamethonium in Treatment of Arteriosclerosis Obliterans

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The effect of hexamethonium on hypertension has been widely studied but its effect on the peripheral blood vessels of patients with severe occlusive vascular disease has been studied on only a few patients although the drug has been used empirically in the treatment of such disease.

Observations were made on the effect of hexamethonium administered subcutaneously in increasing doses of 10 to 50 mg. on the skin temperature of the fingers and toes, the blood pressure and the pulse rates of a group of patients with severe arteriosclerosis obliterans. On this group of patients hexamethonium had little or no effect.

Since hexamethonium was introduced by Paton and Zaimis, its use in the treatment of hypertension has been widely studied, but few authors have reported on its effect on peripheral vascular disease.

The hexamethonium ion causes peripheral vasodilatation by blocking the transmission of nerve impulses across sympathetic ganglia. Schnaper and associates noted that the increase in blood flow in the foot after intravenous administration of 50 to 100 mg. of the hexamethonium ion in 10 normal subjects was not significantly different from that obtained after intrathecal or epidural lumbar anesthesia. This suggested that the degree of blockade of sympathetic vasoconstrictor impulses to the feet was nearly complete after intravenous injection of 50 to 100 mg. of hexamethonium ion. Burt and Graham studied the effect of hexamethonium on five normal subjects, 15 patients with arteriospastic disease, but without occlusive arterial disease and seven patients with hypertension. They noted greater vasodilatation in the lower than in the upper limbs following intravenous injection of 30 to 40 mg. of pentamethonium and hexamethonium ions. The skin temperature of the toes of the normal subjects rose 8.5 C. while that of the patients with vasospastic disease rose 7.9 C. after injection of these drugs. Finnerty and Freis observed the effect of intravenous injection of 20 to 100 mg. of hexamethonium ion on 22 subjects, "some of whom suffered from various types of peripheral vascular disease." In all cases except those of organic obstruction of the larger arteries the skin temperature and blood flow in the digits, particularly in the toes, were markedly elevated. The same authors later reported good clinical results from use of hexamethonium in the treatment of various peripheral vascular diseases, including arteriosclerosis obliterans in five cases. They claimed from their study that it was as effective as paravertebral block. Kvale in a recent review of the treatment of occlusive arterial disease, stated that subcutaneous injections of hexamethonium may be of value in selected cases in which sympathectomy may not be advisable.

The present study was undertaken to evaluate the usefulness of hexamethonium in the treatment of patients with severe arteriosclerosis obliterans.

Method

The observations were made on 14 hospitalized patients who had severe arteriosclerosis obliterans in the lower limbs. There were 12 men and 2 women with an age range of 50 to 78 years, and a mean age of 64 years. Their basal metabolic rates ranged from -28 to +14 per cent.

Data were obtained in a room in which the temperature was 25 to 27 C. and the relative humidity was 40 per cent. The subjects fasted and received no medication of any kind for 15 hours before the test. During the tests they wore lightweight short pajamas and lay supine on comfortable beds. The basal metabolic rate was determined during the control period.

The skin temperature of the fingers and toes was employed as a means of measuring vasoconstriction

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and vasodilatation of the extremities. The temperature of the plantar surfaces of the first, third and fifth toes of both feet and the volar sides of the distal phalanges of the third finger of both hands was measured by means of copper constantan thermocouples. After a control period of about an hour, when the cutaneous temperature had become stabilized and determinations of basal blood pressure and pulse rate had been made, hexamethionium ion was administered subcutaneously. Readings of skin temperature, blood pressure and pulse rate were taken every 5 to 10 minutes for at least 90 minutes. Each patient was given 10 mg. of hexamethionium ion subcutaneously the first day, and it was our intention to increase the dose of hexamethionium ion by 10 to 20 mg. on consecutive days until a dose of 50 mg. was reached. Due to the marked hypotensive effect of the drug on several elderly patients, it was felt unwise to subject them to further episodes of marked hypotension. Thus only 11 of the original 14 patients received 50 mg. subcutaneously.

RESULTS

The findings for the total group of patients are shown in table 1 and in figure 1. In this and following graphs (figs. 2 to 5) the average basal skin temperatures of the three toes and of the fingers before treatment are compared with the average of the maximal responses of the three toes and the fingers to the drug. The pulse rate was increased by 8 to 12 beats per minute following the injections of hexamethionium and the systolic and diastolic blood pressures measured in the supine position decreased 18/9 to 46/22 mm. with increasing doses of hexamethionium. As stated previously the fall in the systolic and diastolic blood pressure after 10 mg. was greater than after 20 to 40 mg. because the three patients could not tolerate larger doses of the drug and thus did not receive them. The skin temperature of the fingers and toes showed little change following injection of 10 to 50 mg. of hexamethionium ion subcutaneously. The drop in blood pressure occurred within 15 to 30 minutes after the injection in all patients, and the skin temperature began to increase during this period in the few patients who showed a response to the drug. The peak skin temperature was reached between one and one-half and two hours after the injection.

Of the total of 14 patients, two had a rise in skin temperature of the toes following the larger doses of hexamethionium, two demonstrated an increase in skin temperature in the less affected lower limb only, and 10 did not show any increase in the skin temperature of the toes following the injections of hexamethionium.

An example of each type of reaction will be shown in the following brief case reports.

Case 1. A white man, 68 years old, complained of a nonhealing ulcer which had been present on the
left great toe for two years. He was otherwise asymptomatic. Examination revealed the pulse in the femoral arteries to be normal. The popliteal pulses were diminished, and pulses were absent bilaterally from the dorsalis pedis and posterior tibial arteries. There was mild pallor on elevation of the legs with dependent rubor. The venous filling time was 45 seconds in the right leg and 35 seconds in the left. A small ulcer was present on the medial aspect of the left great toe. The basal metabolic rate ranged from -21 to -28 per cent during the period of testing.

The response to increasing amounts of hexamethonium is shown in figure 2. The skin temperature in the toes rose sharply even with the smallest dose of the drug, while the skin temperature of the fingers changed less, but definitely, with doses of 30 to 50 mg. of hexamethonium ion. Figure 3 demonstrates the response to 50 mg. of hexamethonium ion. The skin temperature of the toes increased from 26 to 29.3°C, with the peak occurring two hours after the injection. The skin temperature of the fingers increased also, but the rise was not as marked nor as prolonged as that of the toes. Skin temperature studies made after left lumbar sympathetic block with alcohol demonstrated results almost exactly equal to those following administration of 50 mg. of hexamethonium ion subcutaneously.

Case 2. A white man, 59 years old, had bilateral claudication of the calves for three years. Two months before admission spontaneous gangrene of the right great toe developed which necessitated amputation of the toe. The wound failed to heal and an ulcer 1 cm. in diameter was present at the amputation site on admission. All pulses below the femoral arteries were absent bilaterally and mild pallor of both legs was noted on elevation. Dependent rubor was moderate in the right and the venous filling time was 36 seconds in the right and 12 seconds in the left. The response of the skin temperature to hexamethonium is shown in figures 3a and 4. The fingers showed a moderate increase in skin temperature but the skin temperature of the toes did not change even with the larger doses of the drug. The blood pressure usually decreased following injection of hexamethonium.

**FIG. 2 (case 1).** Change in blood pressure and skin temperature in response to increasing doses of hexamethonium ion.

**FIG. 3.** Response of blood pressure and skin temperature to 50 mg. of hexamethonium ion. a. Case 2. b. Case 1.

**FIG. 4 (case 2).** Change in blood pressure and skin temperature in response to increasing doses of hexamethonium ion.

**FIG. 5 (case 3).** Change in blood pressure and skin temperature in response to increasing doses of hexamethonium ion.
Case 3. A white woman, 71 years old, who had had mild diabetes for 12 years, entered the hospital because of an ulcer which had been present for two months on the lateral aspect of the right foot. She had severe constant pain at the site of the ulcer. Physical examination revealed moderate obesity, a nodular goiter, and an ulcer measuring 2 by 1.3 cm. over the right fifth metatarsal. The pulse in the femoral and popliteal arteries was normal bilaterally, as was the pulse in the dorsalis pedis artery on the left. Pulses were absent from the dorsalis pedis and posterior tibial arteries on the right, and from the posterior tibial on the left. There was moderate dependent rubor on the right, but no pallor on elevation. The response of the skin temperature to hexamethonium is shown in figure 5. It will be noted that the skin temperature of the fingers and of the left foot was increased by the larger doses of hexamethonium, but that of the right foot was unchanged. A right lumbar sympathetic block with alcohol was performed, and studies of skin temperature following it revealed no change from the levels obtained prior to the block.

Four of the 14 patients were studied after lumbar sympathetic blocks with alcohol. The skin temperature of the toes of three of these patients had not responded to hexamethonium, nor was it changed by the block. The fourth patient (case 1) demonstrated vasodilation of the toes after both hexamethonium and the alcohol block (figs. 2 and 3b).

Comment

Hexamethonium in the amount given did not cause vasodilatation in the vessels of the lower limbs as measured by skin temperature of the majority of patients with arteriosclerosis obliterans. Since the hypotensive effect of the drug was observed in all patients, vasodilation must have occurred in some other part of the body. Cranley and associates stated that agents used for vasodilation will have their maximal effect on those areas of the body in which the vessels are most nearly normal and a minimal effect on the area in which organic vascular changes have taken place. Our findings are in agreement with this statement. This was well shown in case 3 in which the less severely involved leg showed vasodilation while the skin temperature of the other leg, in which the greatest effect was desired, did not change.

Possibly larger doses of hexamethonium would have been more effective, although Finnerty and Freis found that intravenous injections of 100 mg. of hexamethonium were no more effective in causing vasodilation than 50 mg. We considered that larger doses would be dangerous for patients of the age of our group because of the hypotensive effect.

Patients with early organic vascular disease, in whom collateral vessels are still able to dilate may respond better than the group of patients with severe occlusive arterial disease. It is the latter group, however, which needs treatment, and failure to cause vasodilation with hexamethonium is the rule in this group.

Summary

Hexamethonium ion in increasing doses of 10 to 50 mg. was given subcutaneously to a group of 11 patients with severe arteriosclerosis of the lower extremities. Three additional patients were given 10 mg. but not the larger doses because of the hypotensive effects of the drug. Two patients responded to the drug with a slight to moderate increase in skin temperature of the toes. Two others showed slight vasodilatation in the less ischemic lower extremity, but none in the limb with more severe arteriosclerosis obliterans. The skin temperature of the toes in the remaining 10 patients did not change after the injections of hexamethonium.

From this study it is concluded that hexamethonium is not effective in the treatment of severe arteriosclerosis obliterans. Since the blood pressure decreased after injection of the drug, we assume that vasodilation occurred in blood vessels unaffected by the arteriosclerotic process.

Summario in Interlingua

Ion de hexamethonium esseva administrate subcutaneemente, in doses progressivemente augmentate ab 10 mg usque a 50 mg, a un gruppo de 11 patientes con sever arteriosclerosis del extremitates inferior. Tres altre patientes, originalmente destinate a sequer le mesme curso, recipieva solmente le administrationes de 10 mg. In iste casos le effectos hypotensive del droga esseva si marcate que le dosages augmentate non pareva consiliabile.
Duo patientes reageva per un leve o moderate augumento del temperatura cutanee del digitos del pede. Duo alteres habeva un leve vasodilatation in illo inter lor extremitates inferior que esseva minus ischemic sed non in illo que esseva plus severmente affligite per arteriosclerosis obliterante. In le remanente 10 patientes le temperatura cutanee del digitos del pede non cambiava post le injectiones de hexamethonium.

Ab iste studio nos conclude que hexamethonium non es efficace in le tractamento de sever arteriosclerosis obliterante. Proque le pression sanguinee decreseva post injectiones del droga, nos suppose que vasodilatation occurreva in vasos sanguinee non afficite per le processo arteriosclerotic.

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