THE EFFECTS OF DIHYDROERGOCORNINE ON THE CIRCULATION IN THE EXTREMITIES OF MAN

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Since the advent of therapeutic surgical procedures on the autonomic nervous system, increased interest has been shown in drugs which block this fairly complex and enigmatic part of the nervous system. One of these drugs is a derivative of ergot, called dihydroergocornine (DHO–180). Some of its clinical applications have been reported by several workers, (1–6), showing principally its effects in hypertension, in which a lowering of blood pressure was obtained. Bluntschli and Goetz (2, 5) reported cases in which they recorded toe and finger volume, pulse volume and rate, and skin temperatures before and after administration of dihydroergocornine. They stated that vasodilatation and reduction of blood pressure in both normal and hypertensive subjects were produced through functional blocking of sympathetic impulses by the drug.

Ergot of rye has long been separated into component parts and many substances have been obtained from the crude drug. Stoll and his coworkers (7–9) have shown that ergot contains three alkaloidal groups, and six natural alkaloids, each of which has two isomeric forms. The three groups, and the alkaloids contained therein, are the ergotamine group, containing ergotamine and ergosine; the ergotoxine group, made up of three alkaloids, ergocristine, ergokryptine and ergocornine; and the third group with only one alkaloid, ergobasine. These alkaloids have similar chemical structures and can be transformed into dihydrogenated forms. The latter have been found to be less toxic than the natural alkaloids.

Since dihydroergocornine has been reported to have vasodilator properties by virtue of its purely sympathicolytic action (2, 3, 5, 6), we deemed it interesting to investigate its effects on the peripheral circulatory system in man, under carefully controlled laboratory conditions.

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METHODS

A group of 20 patients with various primary diagnoses, including Ménière's syndrome, multiple sclerosis, headaches of various types and hypertension, volunteered for this study. The ages varied between 20 and 63 years.

Before the observations were begun, the patient reclined quietly on a comfortable test bed for at least 30 minutes, in a constant temperature room at 77° F. with a humidity of about 40 per cent. The blood flow in all four extremities was measured by means of the venous occlusion plethysmograph with a compensating spirometer recorder (10). The arm plethysmograph included the hand, wrist, forearm and part of the arm up to 2 inches (about 5 cm.) above the olecranon process. The leg plethysmograph included the foot, ankle and leg up to 1 inch (about 2.5 cm.) below the tibial tuberosity. Finger and toe pulses were recorded by means of digital plethysmographs on the right and left index fingers and on the right and left second toes.

The heart rate and the systolic and diastolic blood pressures were recorded by means of the usual clinical procedures. Control values were established for heart rate, blood pressure and blood flow before the drug was given. These observations were again repeated at regular intervals during a period averaging 65 minutes and ranging from 15 to 85 minutes after the drug had been administered. However, when the drug was given by infusion over a period of 20 minutes, additional observations were taken during the period of infusion.

Dihydroergocornine was given in total doses from 0.25 mg. to 0.4 mg. The dose varied from 0.0038 mg. to 0.008 mg. per kilogram of body weight. In six cases the drug was given by continuous intravenous infusion in physiologic saline solution containing 0.5 mg. dihydroergocornine (DHO–180) per 100 cc. and was administered over a period of 20 minutes. In 14 other cases the drug was given in a single dose by intravenous injection.

RESULTS

Table I presents the changes in blood flow in the upper and in the lower extremities as well as the changes in heart rate and blood pressure of subjects who were given dihydroergocornine by intravenous infusion in the amounts specified. The average increase in blood flow was 117 per cent for both upper extremities with a range of 35 to

TABLE I

Change in peripheral blood flow, heart rate and blood pressure after dihydroergocornine (DHO-180) had been given by infusion

Case	Total dose	Blood flow, *cc. per min. per 100 cc. of tissue* Arms			Blood flow, *cc. per min. per 100 cc. of tissue* Legs			Heart rate, maximal change	Blood pressure, maximal change	
		Control before injection	Maximal change after injection	Per cent change	Control before injection	Maximal change after injection	Per cent change		Systolic	Diastolic
	mg.							*beats per min.*	*mm. Hg*	*mm. Hg*
1	0.3	3.8	10.0	+163	2.3	3.8	+ 65	− 2	− 5	0
2	0.35	6.4	12.5	+ 95	2.2	3.0	+ 36	− 2	−20	−4
3	0.3	3.2	7.5	+134	2.6	3.3	+ 27	− 6	−20	−4
4	0.4	4.3	5.8	+ 35	3.6	8.6	+139	−12	+28	+4
5	0.35	4.4	13.8	+214	2.6	6.3	+142	−14	−12	−6
6	0.3	4.9	8.0	+ 63	2.6	4.1	+ 58	−12		
Average				+117			+ 78	− 8	− 6	−2

214 per cent. The average increase in both lower extremities was 78 per cent with a range of 27 to 142 per cent. The maximal change in blood flow occurred at an average time of 43 minutes after the infusion had begun and 23 minutes after the entire amount of the drug had been given.

Table II shows the changes in blood flow in the four extremities, as well as the changes in heart rate and blood pressure of subjects given the drug by single intravenous injection. An increase of blood flow was observed in all but one patient. The average increase was 84 per cent with a range of 25 to 170 per cent in both upper extremities. The average increase in both lower extremities was 63 per cent with a range of 8 to 112 per cent. One patient showed a decrease of 3 per cent in the

TABLE II

Change in peripheral blood flow, heart rate and blood pressure after dihydroergocornine (DHO-180) had been given by single intravenous injection

Case	Total dose	Blood flow, *cc. per min. per 100 cc. of tissue* Arms			Blood flow, *cc. per min. per 100 cc. of tissue* Legs			Heart rate, maximal change	Blood pressure, maximal change	
		Control before injection	Maximal change after injection	Per cent change	Control before injection	Maximal change after injection	Per cent change		Systolic	Diastolic
	mg.							*beats per min.*	*mm. Hg*	*mm. Hg*
7	0.35	8.3	11.8	+ 42	3.1	5.3	+ 71	−16	− 2	− 4
8*	0.3	3.0	8.1	+170	2.4	3.9	+ 63	−10	−30	−10
9	0.35	5.3	9.1	+ 72	5.6	8.8	+ 57	−28	−18	−14
10	0.35	5.9	11.7	+ 98	4.5	8.6	+ 91	− 8	+14	+ 6
11	0.25	2.4	5.1	+113	2.4	4.3	+ 79	−32	−16	− 4
12	0.3	9.1	11.4	+ 25	5.9	6.4	+ 8	−10	− 4	+ 4
13	0.35	3.2	4.8	+ 50	1.9	3.4	+ 79	−11	− 6	− 2
14	0.25	6.2	6.0	− 3	3.0	3.4	+ 13	−14	+ 6	+10
15	0.35	5.1	11.4	+124	2.4	4.4	+ 83	−13	−16	0
16	0.3	5.4	10.8	+100	2.5	5.3	+112	−16	−12	+ 2
17	0.3	4.9	6.4	+ 31	2.9	3.5	+ 21	− 2	− 8	−12
18	0.3	3.3	8.3	+152	2.4	3.2	+ 33	−12	− 6	0
19*	0.35	8.7	14.6	+ 68	4.3	8.2	+ 91	−24	−58	−18
20	0.3	4.5	10.4	+131	3.8	7.1	+ 87	−16	− 6	− 8
Average				+ 84			+ 63	−15	− 6†	− 2†

* Hypertensive cases.
† Exclusive of cases 8 and 19.

blood flow of the upper extremities. The overall average increase in blood flow for the entire group of 20 cases was 94 per cent in the upper extremities and 68 per cent in the lower extremities.

At an average time of 65 minutes after the drug had been given, final readings still showed a definite increase in blood flow in all four extremities.

There was no significant change in the systolic or diastolic blood pressure readings in any of the 17 normotensive patients. However, in the two hypertensive subjects (cases numbered 8 and 19 in the tables) there was a significant and marked fall in the blood pressure of both subjects. The maximal change occurred between 30 and 45 minutes after the drug had been given. Tables I and II give the changes of blood pressure on the individual cases.

The heart rate decreased in every case after dihydroergocornine was administered. The average decrease was 13 beats per minute, with a range of 2 to 32 beats per minute. Tables I and II give the changes in heart rate in the individual cases.

No toxic or cumulative effects were noted in the three patients who were given the drug from eight to 20 times once daily on successive days by infusion of 0.5 mg. of dihydroergocornine (DHO–180) in 100 cc. of physiologic saline solution.

Side reactions were common and were noted in 19 of the 20 cases, but none were serious. Seventeen patients complained of nasal congestion, which in most cases produced severe obstruction of the nasal passages. This occurred within 25 minutes after dihydroergocornine had been given and usually lasted for about two hours. Benadryl, given to a few subjects, had no effect on reducing this congestion. Mild to moderate nausea occurred in seven cases and vomiting in only one case. Headache occurred in six cases and was moderately severe. A sensation of flushing occurred for a few minutes in four cases. Four patients experienced a sudden urge to urinate. This occurred at the peak of action of the drug and was not observed in other cases during equally long and similar periods when no drug was given. No flushing of the exposed skin surface nor sweating were noted in any of the cases. No pupillary changes occurred.

Figures 1 and 2 show typical blood flow curves before and at the height of action of the drug. Figure 3 shows the increase over the control in amplitude of the pulse in the fingers and toes after the administration of dihydroergocornine. The pulse tracings of the right and left index fingers and of the right and left second toes of 17

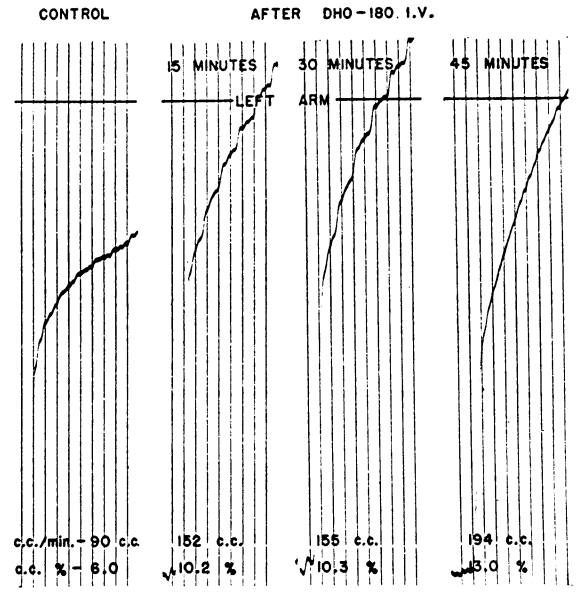

FIG. 1, *a*

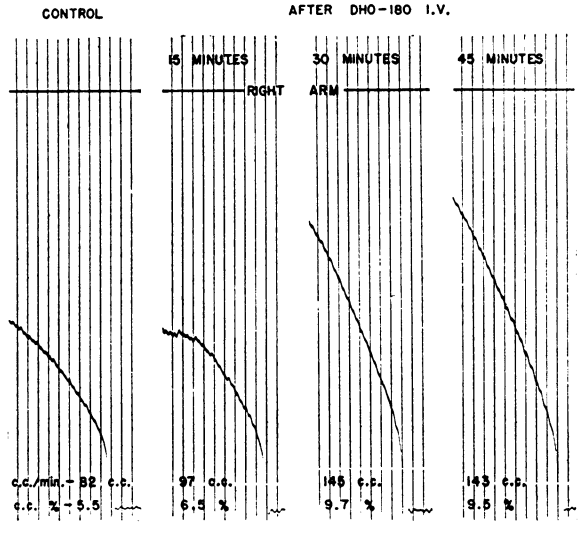

FIG. 1, *b*

FIG. 1, *a* AND *b*. REPRESENTATIVE BLOOD FLOW CURVES BEFORE, AND 15, 30 AND 45 MINUTES AFTER THE INTRAVENOUS ADMINISTRATION OF DIHYDROERGOCORNINE

a, left arm; *b*, right arm.

The curves for the right arm are mirror images of those for the left because each spirometer, as a unit in the compensating mechanism, deflects the beam in the opposite direction.

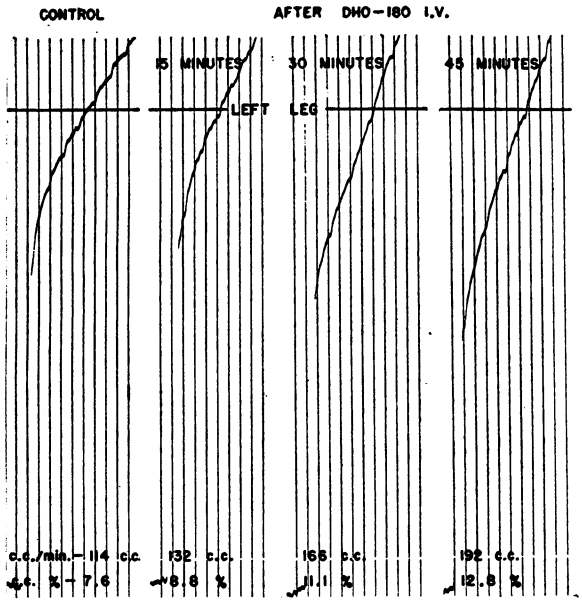

FIG. 2, *a*

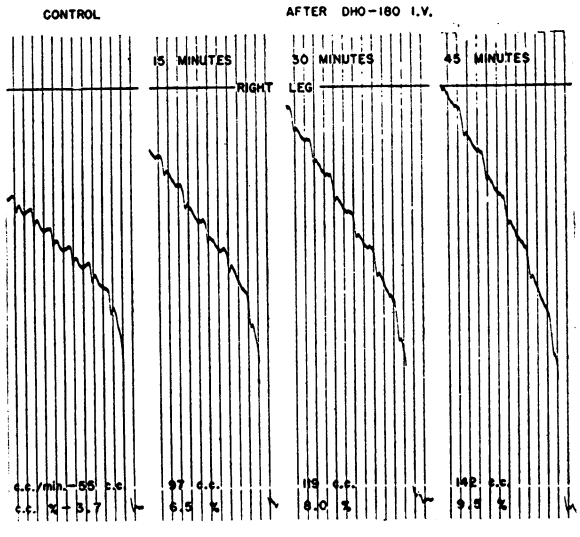

FIG. 2, *b*

FIG. 2, *a* AND *b*. REPRESENTATIVE BLOOD FLOW CURVES BEFORE, AND 15, 30 AND 45 MINUTES AFTER THE INTRAVENOUS ADMINISTRATION OF DIHYDROERGOCORNINE

a, left leg; *b*, right leg.

The curves for the right leg are mirror images of those for the left (see explanation under Figure 1).

of the 20 patients were taken before and at regular intervals after dihydroergocornine had been administered. There was an increase in the amplitude of the pulse in every case—in only one was the increase considered slight. Figure 4 shows the changes in blood pressure, heart rate and blood flow in a representative case.

COMMENT

The mechanisms by which dihydroergocornine exerts its effects are as yet not entirely clear.

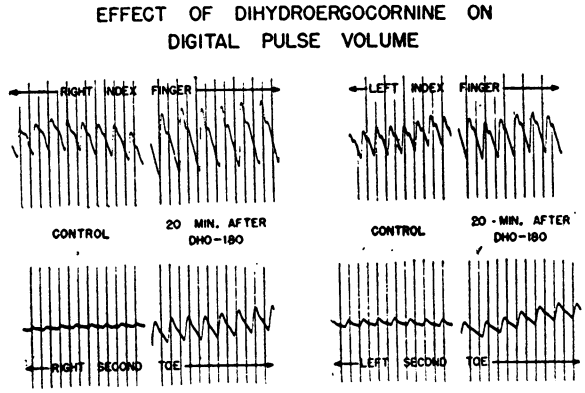

FIG. 3. FINGER-PULSE AND TOE-PULSE VOLUME RECORDINGS BEFORE AND 20 MINUTES AFTER INTRAVENOUS INJECTION OF DIHYDROERGOCORNINE

Note the increase in pulse volume after the drug had been given.

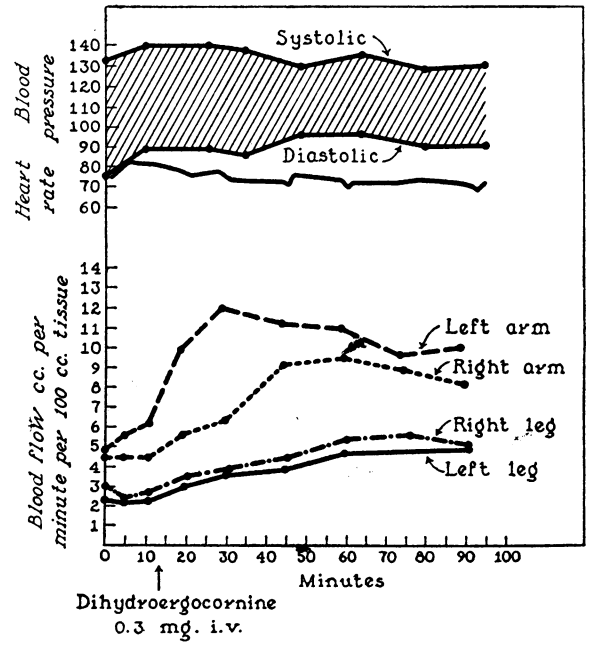

FIG. 4. BLOOD PRESSURE, HEART RATE AND PERIPHERAL BLOOD FLOW BEFORE AND AFTER DIHYDROERGOCORNINE WAS GIVEN INTRAVENOUSLY

Rothlin (11) stated that dihydroergocornine has central and peripheral effects. Its effect on lowering body temperature is of central origin, since it may be blocked by general anesthesia. He further stated that the dihydrogenated alkaloids have a constrictive effect on isolated arteries, blood vessels in the rabbit's ear and in the extremities of the frog. However, in addition to this direct effect on the vessels, there is a latent central sympathicolytic action. He did not observe any visible or latent effects on the isolated heart.

In pithed animals the blood pressure is raised by direct vasoconstrictive action on the vessels, but in the intact animal the blood pressure is lowered and there is a reversal of the epinephrine effect after administration of dihydrogenated alkaloids. Thus the action of dihydroergocornine on the blood vessels in animals is bivalent in that central and peripheral mechanisms are present and act in competition with each other. The fall of blood pressure produced by the natural alkaloids is related to the inhibition of the vasomotor center; the fall in blood pressure produced by the dihydrogenated alkaloids is attributed to stimulation of a vasodilator center. Rothlin (11) attributed the decrease in heart rate to central stimulation of the vagal center.

As is seen from the findings in this study, dihydroergocornine produced an increase in the blood flow in the extremities in all but one case. The increase in blood flow in the extremities is indicated by the plethysmographic findings as well as by the increase in the amplitude of the pulse tracings.

From the studies presented here, no accurate statement can be made as to the site of action of dihydroergocornine. Bluntschli and Goetz (5) presumed the site of action to be "in the medulla and/or hypothalamus."

Side effects in our series were more common than previously reported (1–3, 5, 6) and occurred with lower dosages. Because of this fact we decided against the use of doses larger than 0.4 mg.

Conclusions about cumulative and toxic effects of the drug cannot be made from this study since only three patients were given the drug more than once.

SUMMARY AND CONCLUSIONS

The effects of the intravenous administration of dihydroergocornine, an alkaloid of ergot, on the blood pressure, heart rate and peripheral blood flow were studied on 20 human volunteers. The drug was administered to six patients by intravenous infusion of a solution containing 0.5 mg. of dihydroergocornine per 100 cc. of physiologic saline solution, and to 14 patients by a single intravenous injection. The total dose varied from 0.25 mg. to 0.4 mg. The blood flow was determined by means of a venous occlusion plethysmograph with the compensating spirometer recorder.

Dihydroergocornine produced an over-all average increase in peripheral blood flow of 94 per cent in the upper extremities, and 68 per cent in the lower extremities. In one case the blood flow in the upper extremities decreased 3 per cent.

The blood pressure fell in the two hypertensive cases after administration of dihydroergocornine. In normotensives there was no significant change in blood pressure.

The heart rate decreased in every case with an average reduction of 13 beats per minute.

Side reactions were more common than previously reported even with lower dosage. Nasal congestion, nausea, headache, flushing, an urgency for urination and vomiting were the side reactions observed.

BIBLIOGRAPHY

1. Bluntschli, H. J., Clinical observations on the sympathetic inhibitory effects of a new ergot alkaloid. South African M. J., 1947, **21**, 21.
2. Bluntschli, H. J., and Goetz, R. H., The effect of a new sympathicolytic drug (dihydroergocornine) on the blood-pressure with special reference to hypertension. South African M. J., 1947, **21**, 382.
3. Wilkins, R. W., Freis, E. D., and Stanton, J. R., Essential hypertension; laboratory studies in human beings with drugs recently introduced. J. A. M. A., 1949, **140**, 261.
4. Tandowsky, R. M., and Cerini, F. V., High blood pressure aids. Science News Letter, 1948, **53**, 404.
5. Bluntschli, H. J., and Goetz, R. H., The effect of ergot derivatives on the circulation in man with special reference to two new hydrogenated compounds (dihydroergotamine and dihydroergocornine). Am. Heart J., 1948, **35**, 873.
6. Freis, E. D., Stanton, J. R., and Wilkins, R. W., The effects of certain dihydrogenated alkaloids of

ergot in hypertensive patients. Am. J. M. Sc., 1948, **216**, 163.

7. Stoll, A., and Hofmann, A., Die Alkaloide der Ergotoxingruppe: Ergocristin, Ergokryptin und Ergocornin. Helvet. chim. acta, 1943, **26**, 1570.
8. Stoll, A., Hofmann, A., and Becker, B., Die Spaltstücke von Ergocristin, Ergokryptin und Ergocornin. Helvet. chim. acta, 1943, **26**, 1602.
9. Stoll, A., and Hofmann, A., Die Dihydroderivate der natürlichen linksdrehenden Mutterkornalkaloide. Helvet. chim. acta, 1943, **26**, 2070.
10. Berry, M. R., Baldes, E. J., Essex, H. E., and Wakim, K. G., A compensating plethysmokymograph for measuring blood flow in human extremities. J. Lab. & Clin. Med., 1948, **33**, 101.
11. Rothlin, E., The pharmacology of the natural and dihydrogenated alkaloids of ergot. Bull. schweiz. Akad. d. med. Wissensch., 1947, **2**, 249.