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Cardiovascular Evaluation of a Pressor Amine (Tetrahydrozoline) Showing Hypotensive Properties in Man.*† (22951)

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Hutcheon and his colleagues(1) found that in animals, tetrahydrozoline (2-(1.2.3.4-tetrahydro-1-naphthyl) imidazoline hydrochloride) caused an increase in arterial pressure similar to that produced by epinephrine. However, it differed qualitatively from the epinephrine effect in that onset of hypertension was slower and its duration was more prolonged. Increase in blood pressure caused by tetrahydrozoline was diminished, but was never reversed by adrenolytic agents such as phentolamine. The sympathomimetic effect of tetrahydrozoline in animals was so striking that these investigators suggested evaluation of this drug as a pressor agent in certain hypotensive states.

Despite this report(1), preliminary studies in our laboratory indicated that tetrahydrozoline *reduces* blood pressure in man. The present study was undertaken to clarify the hypotensive effect of this sympathomimetic amine.

Methods and materials. The patients in this study were from the medical wards and the hypertensive clinic of the District of Columbia General Hospital. All ward patients who received the drug by injection underwent complete clinical and laboratory studies. In the clinic, where the patients received tetrahydrozoline by mouth, they were examined at least at weekly intervals and more commonly twice a week for the first month. It was possible to follow 30 of the 42 patients over a 2 to 3 week period on placebo therapy. The hemodynamic studies were carried out on hospitalized patients who were in the fasting basal state. Cardiac output was measured with indicator-dilution curves using Evans Blue dye(2). Serial studies were performed at least 20 minutes apart to assure complete mixing of the dye. Arterial pressure was recorded by the auscultatory method. The average of systolic and diastolic pressures was taken as mean arterial pressure. Total peripheral resistance was calculated by dividing mean arterial pressure by cardiac output (ml/min). Venous pressure was measured using a saline manometer in an antecubital vein at the level of the right auricle.

Results. Blood pressure changes following tetrahydrozoline given intravenously. Forty-two patients received tetrahydrozoline intravenously (0.5 mg to 2 mg, average 1.5 mg). In 17 patients, a pressor response was noted (average 35%), beginning less than 30 seconds after injection, reaching its peak within 3 minutes. (Early in this investigation, an immediate pressor response was not specifically looked for, so the actual frequency of this transitory phenomenon cannot be determined accurately. More recent experience indicates that an immediate pressor response consistently follows tetrahydrozoline given intravenously.) A 32% fall in heart rate ac-

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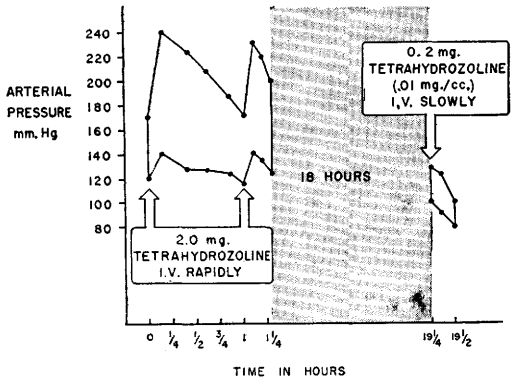

FIG. 1. Chart of arterial pressure of patient G. G. demonstrating response to large and small doses of tetrahydrozoline.

companied the hypertensive response in these 17 patients. The pressor period was accompanied by no symptoms.

Fifteen to 20 minutes following administration of parenteral tetrahydrozoline, arterial pressure and heart rate had usually returned to control level. This was followed by a hypotensive phase, which usually began 20 to 30 minutes (average 25 minutes) following initial injection. The peak of hypotensive response was 2.5 to 3.5 hours. Duration ranged between 4 to 12 hours (average 6 hours). During this latter period there was an average fall in systolic pressure of 31 mm Hg (range, 10 to 40 mm Hg). The heart rate decreased an average of 17 beats per minute (range 0 to 50).

Six patients received tetrahydrozoline intramuscularly (0.5 mg to 1 mg). Onset of hypotensive effect in these patients averaged 45 minutes, the peak of action was 2 to 3 hours and duration 6 to 7 hours. Four patients were treated for 5 days. No refractoriness developed during this period.

Differences between large and small parenteral doses were studied as follows: 2 mg tetrahydrozoline were administered rapidly intravenously (Fig. 1). Within 30 seconds, a 24% increase in mean arterial pressure and a 25% decrease in heart rate occurred. In one hour, when arterial pressure had returned to the control level, intravenous injection of 2 mg tetrahydrozoline was again immediately followed by a pressor response. Eighteen hours later, mean arterial pressure was 20% below the control level. A dose of 0.2 mg (20 ml tetrahydrozoline in concentration of 0.01 mg/ml) administered over a 5 minute period was followed in 15 minutes by further fall in arterial pressure (48% reduction). No pressor phase preceded this hypotensive response.

The reverse of this experiment in another patient gave similar results. Tetrahydrozoline 0.2 mg intravenously was followed in 25 minutes by a 17% fall in arterial mean pressure and a 20% fall in heart rate. In 2 hours, when arterial pressure had returned to control level, repeated intravenous injection of 2 mg of tetrahydrozoline was immediately followed by a 24% increase in arterial mean pressure and 20% decrease in heart rate.

Blood pressure changes following tetrahydrozoline given orally. Tetrahydrozoline was administered orally to 34 moderately severe hypertensive patients. The average effective dosage was 6 to 15 mg/day, given in divided doses. Duration of treatment varied from 4 weeks to 24 weeks (average 14 weeks), except in 2 patients in whom side effects necessitated stopping the drug after 2 weeks. No patient exhibited a hypertensive response. Seven patients had no hypotensive effect either. In 27 patients there was an average fall of systolic pressure of 26 mm Hg (range, 10 to 120 mm Hg). Hypotension was usually accompanied by bradycardia. Although no fall in heart rate was seen in 5 patients, there was an average reduction of 20 beats/minute in 28 patients (range 2 to 46 beats/minute).

A sustained reduction in blood pressure beyond a 10-week period was seen in only 6 patients. Tolerance developed in the remainder of the 21 patients. Once tolerance developed, increasing the dosage to 3 or 4 times the previous level did not cause a hypotensive effect. When the drug was discontinued for a week or 10-day period, a hypotensive effect was again witnessed in the previously effective dosage range.

When placebo therapy was substituted for tetrahydrozoline, a rise in arterial pressure to control level, or higher than control level, was witnessed in each patient.

Cardiac output and total peripheral resis-

TABLE I. Hemodynamic Changes Immediately Following and One Hour after Intravenous Administration of Tetrahydrozoline in 3 Patients.

	% change from control to 1 min.				% change from control to 1 hr			
	CO	MAP	HR	TPR	CO	MAP	HR	TPR
	−40	+28	−47	+57	−23	−76	−16	− 5
	−47	+26	−23	+62	− 9	−26	+19	−19
	−22	+41	−42	+55	−51	−40	−11	− 8
Avg	−36	+32	−37	+58	−28	−47	−14	−11

CO = Cardiac output. MAP = Mean arterial pressure. HR = Heart rate. TPR = Total peripheral resistance.

tance. Administration of 0.5 mg to 1 mg of tetrahydrozoline intravenously in 3 patients produced an early and transitory pressor response, as noted above. During this phase there was an increase of 32% in mean arterial pressure, 36% fall in cardiac output, 37% decrease in heart rate, and 58% increase in total peripheral resistance (Table I). One hour from the time of injection of tetrahydrozoline (approximately 40 minutes after the pressor effect) mean arterial pressure had decreased an average of 47%. This reduction in arterial pressure was accompanied by a decrease of 28% in cardiac output and a return of heart rate towards normal (decrease from control value 14%). During the hypotensive phase there was a decrease in total peripheral resistance of 11% below control level.

In 6 subjects receiving tetrahydrozoline orally, a reduction of mean arterial pressure from an average of 171 mm Hg to 143 mm Hg (15%) was accompanied by no significant change in cardiac output and a 20% reduction in total peripheral resistance.

Preliminary studies showed that tetrahydrozoline produced no consistent alteration in the cold pressor response or alteration of the pressor response to adrenalin. Thus, no ganglioplegic or adrenolytic activity was detected.

Bradycardia due to tetrahydrozoline was abolished by administration of 60 to 120 mg of atropine sulfate intravenously in 5 patients, indicating that the bradycrotic effect of the drug was probably mediated by the vagus nerve.

No consistent change in venous pressure was seen following tetrahydrozoline administration, during either pressor or hypotensive phases. Except for slowing of heart rate and increase of PR interval in 3 patients, no significant changes were found on the electrocardiogram during the pressor or hypotensive phases of the drug.

Discussion. The di-phasic action of tetrahydrozoline on circulation resembles the di-phasic action of epinephrine(3,4). Tetrahydrozoline, like epinephrine appears to possess excitatory and inhibitory properties; the excitatory component causes vasoconstriction and the inhibitory component, decrease of vascular tone. The high initial concentration of the drug causes vasoconstriction; when the excitatory action has worn off, a sufficient concentration of tetrahydrozoline to cause vasodilation may still be present. The pressor effect immediately following the administration of 2 mg of tetrahydrozoline and lack of a pressor response following slow administration of 0.2 mg tetrahydrozoline support this interpretation of the action of the drug (Fig. 1).

According to this concept, parenteral administration of tetrahydrozoline is followed immediately by a hypertensive phase (high concentration in blood) of short duration. The hypotensive phase (minimal blood concentration) continues for that period of time necessary for complete excretion of the drug and therefore is of fairly long duration. Lack of a pressor response following oral administration of tetrahydrozoline can best be explained by lack of complete absorption resulting in low blood concentrations. It is hoped that these studies will stimulate investigation of related drugs for their anti-hypertensive properties.

Summary. 1. Seventeen of 42 patients who received tetrahydrozoline intravenously exhibited an immediate pressor response which lasted an average of 12 minutes. Twenty-five minutes following the initial injection hypotension ensued, lasting an average of 3 hours. The pressor phase was characterized by a decrease in cardiac output, bradycardia and an increase in total peripheral resistance. The hypotensive phase was

characterized by no change in cardiac output, less bradycardia than in the pressor phase, and a decrease in peripheral resistance. 2. When tetrahydrozoline was administered orally, no pressor response was noted. Twenty-seven of 34 patients exhibited an average reduction of 44 mm Hg systolic pressure, 25 mm Hg diastolic pressure, and an average decrease in heart rate of 20 beats per minute. Tolerance usually developed in 7 to 10 weeks.

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Human Liver Succinoxidase.* (22952)

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This report deals with conditions necessary for maximum succinoxidase activity in human liver homogenates, the distribution of succinoxidase in subcellular components of human liver and the range of normal for whole homogenates of human liver when "standard conditions" are used(1) and when optimum conditions are used. Waterlow(2), using the Cartesian diver technic, found one-tenth the activity obtained during the present study. Davis *et al.*(3) recently reported succinoxidase Qo_2/mg (dry weight) of slices. The thickness of the slices was not indicated. The incubation medium was not specified beyond saying that Krebs-Ringers succinate was used. A "standard technic" is referred to(1), but this gives only a method for homogenates of small animal tissues and not for human liver slices. How important is it to specify the exact conditions used for measuring succinoxidase activity or to use optimum conditions? What can be considered a normal level of activity? These are questions which led to the following work.

Materials and methods. The selection of patients for biopsy and the preparation of tissue have been described(4). 'Sediment' as used below indicates all particulate matter in a whole homogenate which is sedimentable at 10,000 × g for 30 minutes with one washing in isotonic sucrose. The reaction mixture used initially was that recommended by Umbreit(1). Standard manometric technics were used with an equilibration period of 10 minutes. Readings were taken for 70 minutes. The reaction was zero order for this period. As the optimum level of each constituent was determined this level was substituted in all subsequent experiments until a final optimum reaction mixture was obtained. Using these optimum conditions, variation of cytochrome c and substrate concentrations were restudied. The pH of the reaction mixtures was determined with a Beckman model G pH meter before and immediately after the experiment was completed. The cytochrome c† and sodium succinate were commercial preparations. Ascorbic acid was used for determination of cytochrome oxidase activity. The manometric analyses, including controls for endogenous respiration, were carried out at least in duplicate. The average endogen-

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† Standardization of cytochrome c was spectrophotometrically(1). For an assumed molecular weight of 13,000, various shipments of cytochrome c from Nutritional Biochemicals Co., Cleveland, O., proved to be from 52 to 60% pure. This material gave the same optimum concentration of cytochrome c for rat liver succinoxidase as has been reported(5).