Hypotensive Action of Progesterone in Experimental and Human Hypertension. (25282)

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Considerable evidence has accrued to suggest that disturbed electrolyte metabolism may be one of the factors in arterial hypertension. When treating hypertensive patients many physicians employ measures to reduce the body's content of sodium chloride with the feeling that this will be of benefit whether it is induced by dietary salt restriction, natruretic drugs, or oral cation exchange resins. Genest *et al.*(1) produced evidence to suggest that aldosterone production may be increased in essential hypertension. This could be a part of the mechanism whereby hypertensives retain sodium. Progesterone has been shown by Landau *et al.*(2) to possess not only natruretic properties in normal persons but to oppose the salt retaining influence of aldosterone *in vivo*(3). It appeared worthwhile to assess the influence of progesterone on high blood pressure in experimental animals and in humans with essential hypertension.

Methods and materials. Rats. Growing male rats of the Long-Evans strain were subjected to left nephrectomy and loose ligature of the right renal artery according to the method of Kempf and Page(4). Rat systolic blood pressures were determined by the method of Friedman and Freed(5). Pressures were recorded daily at 8 a. m. before injection of progesterone or placebo and at 4, 6, and 8 hours after injection. Of 2 male mongrel dogs used, one had been rendered hypertensive by wrapping its kidneys in silk to induce perinephritis after the method of Page(6). The other had silica injected into the renal arteries after the method of Moses(7). Blood pressures were determined daily by direct needle puncture of femoral artery and recorded by mercury manometer. Both dogs served as their own controls having been observed to maintain a reasonable elevation of blood pressure for some months before progesterone was administered. Human subjects with a diagnosis of primary arterial hypertension were admitted to the metabolic ward of Lilly research unit in Marion County General Hospital. All patients had been attending the hospital out-patient clinic for several years during which time all known causes for secondary hypertension had been thoroughly excluded. No patient had blood urea above normal. Each patient was given a 1½ g sodium diet, and total intakes of sodium and potassium were calculated daily. Twice daily injections, initially of placebo, later of progesterone, and finally of placebo were given into alternate buttocks throughout hospitalization. Substitutions of placebo for progesterone and vice versa were made without the patients' knowledge. These patients were allowed up but were made to rest in bed for 15 minutes before each blood pressure determination. Blood pressures in lying and standing positions were determined 6 times daily from 6 a.m. at 3 hourly intervals until 9 p. m. Stools were not analyzed for electrolyte content, but daily 24-hour urine specimens were collected and analyzed for sodium, potassium, chloride, and creatinine. Sodium and potassium were estimated by flame photometry using an internal lithium standard, chloride by the Van Slyke modification of Volhard's method(8), and creatinine by the method of Bosnes and Fanasky(9). Three women whose blood pressure remained within the hypertensive range after several days of dietary and placebo treatment were retained in the hospital for trial of progesterone. One man was retained in the series even though his blood pressure fell almost to normal with only dietary and placebo treatment. It was thought worthwhile to study the effects of progesterone on at least the electrolyte metabolism of a hypertensive human male. In all species, progesterone used was Injection progesterone U.S.P., 50 mg/cc.* Each cc contains progesterone 50 mg in peanut oil, with benzyl benzoate 20% and preservative phenol 0.5%. The placebo

* Supplied by Eli Lilly and Co.

TABLE I. Observations on Patients before, during, and after Administration of Progesterone.

Patient	Before treatment with progesterone			During treatment with progesterone				After treatment with progesterone		
	Days of placebo treatment	Blood pressure		Days of progesterone treatment	Daily dosage of progesterone	Blood pressure		Days of placebo treatment	Blood pressure	
		Lying	Standing			Lying	Standing		Lying	Standing
G.M.	5	187/116	187/125	15	300	152/100	136/97	6	187/113	168/121
N.H.	5	176/117	153/113	14	150	141/102	115/89	17	158/105	130/100
E.C.	6	185/107	173/106	14	300	150/ 96	138/93	16	159/112	152/ 98

* All blood pressures (arterial, in mm Hg) are avg of 12 determinations during last 2 days of indicated periods. Durations of these treatment periods varied as indicated, no changes in treatment being made until B.P. had remained reasonably constant for 2 days.

material* differed from this only in that it contained no progesterone.

Results. Rats. Five of 6 hypertensive rats, given progesterone 15 mg/kg subcutaneously once a day for 4 days, exhibited reduction in systolic blood pressure from a high pretreatment level (avg. 181 mm Hg for 5 rats) down to much lower levels (avg. 148 mm Hg for 5 rats). Many individual readings were below this figure in the region of 140 mm Hg. Reduction of blood pressure was not noticeable until second day of progesterone treatment (Fig. 1), and became maximal by the end of third day. The sixth rat failed to respond. Its blood pressure had been within 200 to 220 mm Hg range for some months and had previously responded only minimally to several other drugs. The data pertaining to this animal were not used in Fig. 1. Without exception blood pressures of the 5 responsive rats returned to high pretreatment levels within 2 days after discontinuing progesterone. Three more hypertensive rats were used as controls and received 4 daily injections of placebo. The average of their blood pressures remained at all times within the range of 180 to 185 mm Hg (Fig. 1). These rats were later responsive to progesterone.

After a 3-day interval, progesterone injections were repeated during another 4 days (Fig. 1). The resulting fall in blood pressure was slightly less but of the same order as before (Fig. 1).

To test whether rats might become refractory to the hypotensive influence of progesterone, a long term experiment was also undertaken. Three rats were injected daily for 4 weeks with 15 mg/kg of progesterone. With exception of the first 2 days, their blood pressures were reduced to 150 mm Hg range during the entire 4 weeks. Although their blood pressures fluctuated from day to day and from week to week, no trend towards refractoriness was seen; and the lowest average pressure for any one week occurred during the last week. All blood pressures promptly returned to the high pretreatment levels within 2 days of stopping treatment.

Dogs. Both hypertensive dogs showed considerable reduction in blood pressure at time of progesterone administration (20 mg/kg

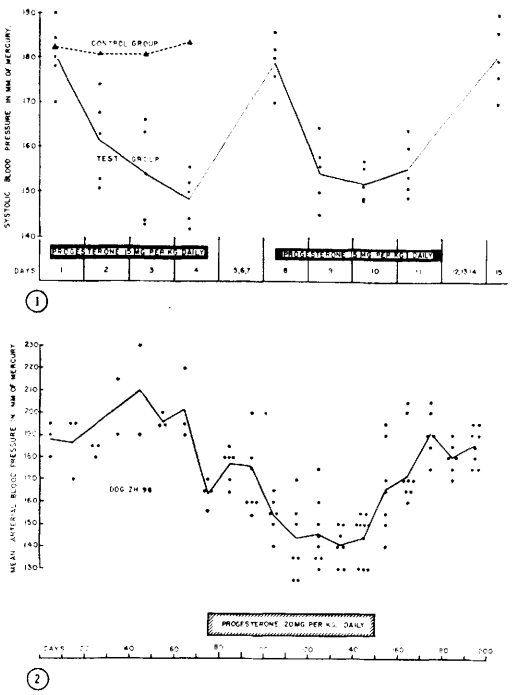

FIG. 1. The effect of progesterone on the blood pressure of hypertensive rats. Each triangle represents daily avg of 4 blood pressures (B.P.) in all 3 rats treated with placebo injections. Each dot represents daily avg of 4 B.P.'s in individual rats of the progesterone treated group of 5 animals. Lines are drawn through daily avg B.P. for all rats in a group.

FIG. 2. The effect of progesterone on the blood pressure of a hypertensive dog. Each dot represents a single blood pressure (B.P.) determination in dog ZH 96. The line passes through the avg B.P. of 10-day periods.

daily), which was maintained until treatment was stopped (Fig. 2). Changes in dog blood pressures occurred only slowly during the course of weeks, in contrast to the rapid changes which occurred in rats. Fig. 2 relates to one of the dogs and is typical of the response in both animals.

Humans. A reduction in B.P. occurred in all 3 women at time of progesterone treatment (Table I). Without exception, their pressures increased again after reinstitution of placebo treatment. Fig. 3 relates to one of these patients, and her response was typical of all 3 women. Blood pressures reached their lowest level only after 10 to 12 days of progesterone treatment, and this might appear to have followed natruresis and the establishment of a new sodium equilibrium. That standing blood pressures were reduced more than lying blood pressures is also suggestive indirect evidence that the fall was secondary to natruresis.

After placebo was substituted for progesterone, every patient retained sodium in amount about equal to that lost at time of progesterone treatment. Blood pressures did not rise again until this retention was almost complete. In patient G. M., a second series of progesterone injections was given following a cycle such as illustrated by Fig. 3. Only 150 mg of progesterone once daily was given during this second period, and this resulted in less salt loss and a smaller and slower fall in blood pressure than had followed the higher dosage. Refractoriness, shown by sodium retention and rising bood pressure, developed after 14 days. The situation was brought under control promptly after progesterone dosage was doubled to 150 mg twice daily.

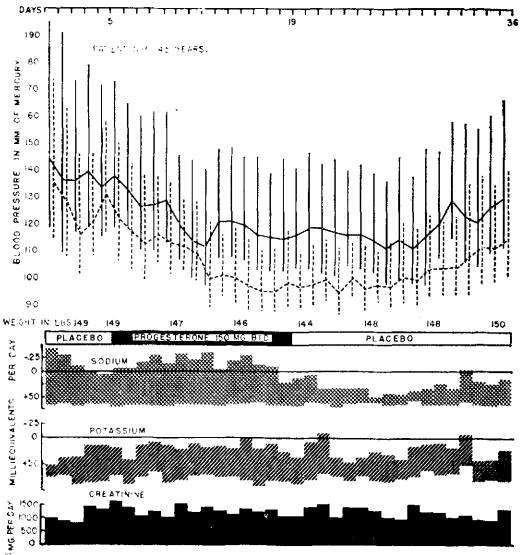

FIG. 3. Hypotensive and natruretic responses to progesterone of a woman suffering from essential hypertension. Tops of vertical bars represent avg of 6 systolic blood pressures (B.P.) in one day while bottoms represent avg of the 6 diastolic B.P.'s. Black bars refer to lying B.P. and interrupted bars to standing B.P. Mean B.P. (diastolic pressure plus ⅓ of pulse pressure) from day to day indicated by lateral lines. Milliequivalents of sodium and potassium passed in 24-hr urines are related to calculated dietary intake. Dietary intake indicated by distance of base of column below zero line. Sodium and potassium columns not reaching zero line represent negative balance.

Immediate natruresis and a slow continuous reduction of blood pressure resulted.

The only man in this series became virtually normotensive during initial control period of placebo treatment. However, he did exhibit a convincing natruresis in response to progesterone which, as in the case of the women, was abruptly followed by sodium retention the day after placebo was substituted for progesterone. His blood pressure changes during progesterone treatment, although necessarily too small to be of significance, were at least in the right direction to be consistent with the response observed in the women.

Discussion. Administration of progesterone to both rats and dogs with experimental hypertension and to human subjects with primary arterial hypertension coincided with a considerable lowering of blood pressure.

The hypotensive action of progesterone in humans might well have been secondary to natruresis. No electrolyte studies were carried out in the animals to study this point.

No refractoriness to progesterone was encountered when dosage was 150 mg twice daily, but it was evident in one patient (G. M.) after 14 days of progesterone at half this dosage.

Even when the daily average of all 6 blood pressures was almost within the normotensive range, single very high pressures in response to emotion were occasionally observed. Such an observation is consistent with there being more than one factor involved in the mechanism of hypertension.

A disadvantage in the use of progesterone was pain at injection sites. This pain was just as evident following placebo and presumably depended upon the bulky nature of the injections. Another disadvantage was the expected fourth day "withdrawal bleeding" experienced by the women after progesterone was discontinued. One woman had her normal menses, no heavier than usual, actually during progesterone treatment. Withdrawal bleedings were no longer nor more copious than the usual menses of these women. Impotence in men following progesterone administration has been reported(10), but the only man in this series had been impotent for some years and experienced no change in this respect after receiving progesterone.

No body depletion of potassium occurred with progesterone induced natruresis, and potassium was even to some small extent retained at this time. In this respect, progesterone appears to have an advantage over natruretic and kaluretic agents such as mercurial diuretics and chlorothiazide.

In no animal or human were blood pressures reduced by progesterone to below normal levels.

Even with these advantages, however, it is not implied that progesterone should be generally used in treating human arterial hypertension. Withdrawal bleeding in women, impotence in men, and painful bulky injections make it impractical.

Summary. (1) Progesterone administration to rats and dogs with experimental hypertension and to humans with primary arterial hypertension resulted in a decline in blood pressure levels. Blood pressures increased once more in all cases after progesterone was discontinued. (2) In humans, but not necessarily in rats and dogs, blood pressure reduction would appear to have resulted from natruresis.

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