Evaluation of Antihypertensive Drugs in Dogs with Angiotensin-Induced Hypertension (35382)

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Despite intensive efforts to evaluate antihypertensive drugs in laboratory animals, a number of agents were first shown to possess activity in man. Although numerous laboratory models have been devised in attempts to assess antihypertensive efficacy it is now generally thought that a model possessing an elevated blood pressure is to be desired (1). Accordingly, a variety of hypertensive models have been created, some of which are based upon the use of genetically bred hypertensive strains of rats (2–4), unilateral nephrectomy in dogs and rats usually accompanied by additional pharmacological or surgical manipulation of the contralateral kidney (5, 6), the daily administration of deoxycorticosterone for extended periods of time (7), neurogenically-induced (8), and pinealectomy-induced hypertension (9), among others. These models, though useful, all require time prior to the development of elevated blood pressures.

Accordingly, we report our preliminary results inducing acute hypertension in dogs by the constant infusion of angiotensin II, and the results obtained with three known antihypertensive drugs, hydralazine, sodium nitrite, and hexamethonium.

Methods. Mongrel dogs of either sex were anesthetized with pentobarbital sodium (30 mg/kg, ip). Blood pressure (BP) was recorded via an indwelling femoral arterial catheter attached to a P23AC Statham pressure transducer, and a permanent record was made on a direct writing polygraph. Following an initial control period, two groups of experiments were performed on a total of 30 dogs. In the control group, either hydralazine, sodium nitrite, or hexamethonium was administered once, in a single dose of 10 mg/kg, iv. In the second group, angiotensin II was infused into the contralateral femoral vein at a constant rate, so that systolic blood pressure was elevated at least 50 mm Hg. This required an infusion of approximately 75 ng/min/animal. Thirty min following the beginning of this infusion, a single dose of 10 mg/kg, iv of either hydralazine, sodium nitrite, or hexamethonium was administered. All drug solutions were freshly prepared each day.

Results. Figure 1 illustrates the mean responses observed following the administration of three different hypotensive drugs in normotensive anesthetized dogs. As shown, following hydralazine, systolic BP continued to rise steadily for the next 50 min from an initial mean level of 137 to 172 mm Hg, and diastolic BP fell initially from a control of 82 to 63 mm Hg shortly after administration. However, after the 10-min level, diastolic BP continued to rise and approximated the control reading at +50 min. Thus, in the presence of normotension, the iv administration of hydralazine was characterized by a rather transient fall in diastolic BP, a prolonged elevation of the systolic BP, and the mean arterial BP was therefore elevated (105 vs 127 mm Hg).

The blood pressure responses elicted by sodium nitrite and hexamethonium in anesthetized normotensive dogs are also shown in Fig. 1. Sodium nitrite lowered systolic BP from a control of 131 to 92 mm Hg, and diastolic BP from 62 to 55 mm Hg at +20 min. Thereafter, both systolic and diastolic continued to rise, although systolic BP never exceeded the initial control level.

Hexamethonium produced a pronounced fall in systolic BP from a control of 136 to 97 mm Hg, and a diastolic fall from 76 to 50

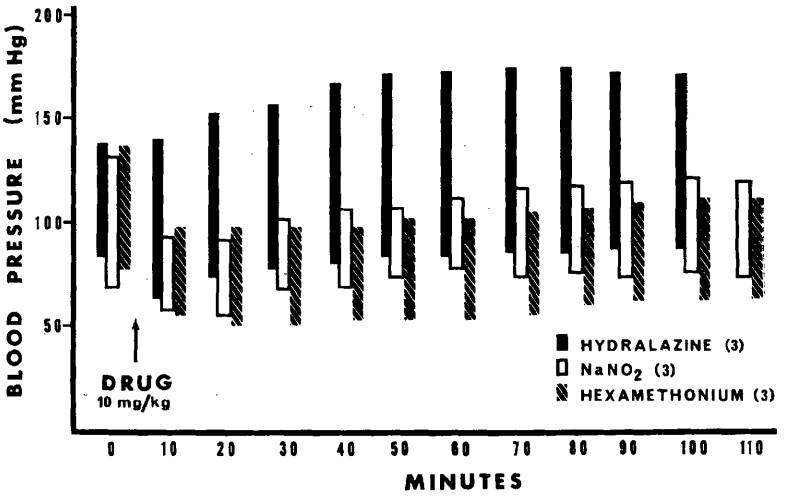

FIG. 1. Mean blood pressure responses in the anesthetized dog to hydralazine, sodium nitrite ($NaNO_2$) and hexamethonium: Number of animals is given in parentheses.

mm Hg at +20 min. Thereafter, both systolic and diastolic BP rose, though neither ever returned to the initial control levels.

Figure 2 illustrates the results obtained in the group exposed to angiotensin II infusion. The mean results of five control dogs show that a constant infusion of angiotensin II raised systolic BP from a control of 125 to 191 mm Hg, and diastolic BP from 72 to 135 mm Hg at +70 min. The relative stability of this elevated systolic and diastolic BP attests to the fact that, with a constant infusion over a 2-hr period, tachyphylaxis does not appear.

Thirty min after angiotensin II infusion was begun, the three antihypertensive agents were administered, again in a single dose of 10 mg/kg, iv. Under these conditions the administration of hydralazine produced a slight, but transient fall in systolic BP and a

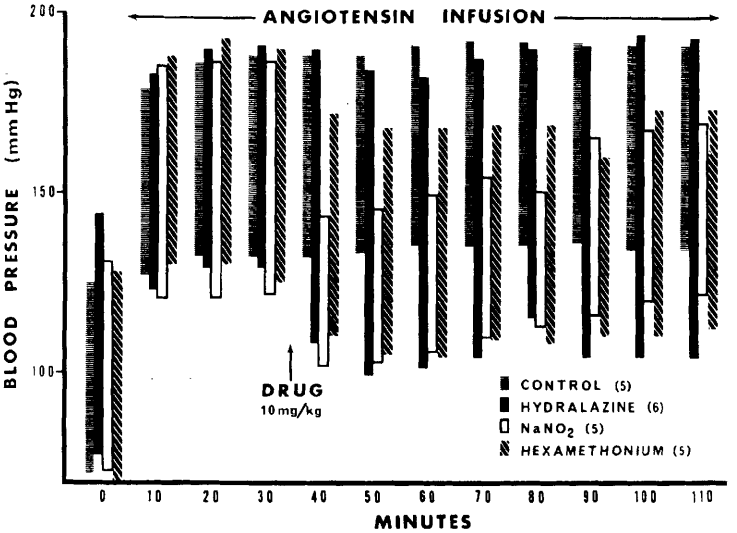

FIG. 2. Mean blood pressure responses in the anesthetized dog: Angiotensin II administered by constant iv infusion, and hydralazine, sodium nitrite ($NaNO_2$) and hexamethonium given as indicated: Number of individual experiments is given in parentheses.

marked fall in diastolic BP which persisted throughout the experiment. However, by +100 min systolic BP had crept back to predrug levels. Nevertheless, if one compares the prehydralazine BP levels at +30 min (191/125) to the posthydralazine levels at +100 min (193/105) it is apparent that hydralazine has a prolonged and significant effect upon the diastolic BP, even though the mean arterial BP only fell from 158 to 149 mm Hg. Thus, the antihypertensive effect of hydralazine was unmasked in the presence of an elevated BP.

The administration of sodium nitrite and hexamethonium in the presence of angiotensin-induced hypertension is also illustrated in Fig. 2. Again, the peak depressor effect of sodium nitrite occurs very shortly after administration (186/121 to 144/102) with both systolic and diastolic BP rising slowly thereafter, although neither ever reached predrug levels before the experiment was terminated.

The results with hexamethonium are of interest because in the presence of angiotensin-induced hypertension, the systolic BP never fell below that produced by sodium nitrite, whereas it did in the absence of angiotensin (see Fig. 1). Although the significance of this observation is unclear, hexamethonium produced a significant hypotensive reponse (195/126 to 167/105) reaching its low point at +50 min.

Discussion. These results suggest that certain antihypertensive drugs (*e.g.*, hydralazine), can be shown to produce depressor responses in the presence of an elevated blood pressure. Indeed, in normotensive dogs, the administration of hydralazine resulted in an increase in both systolic and mean arterial blood pressure.

It is possible that the increase in systolic blood pressure produced by hydralazine in the normotensive animal was the result of a direct action upon the heart. That this possibility exists is suggested by the fact that propranolol can attenuate peripheral vascular and cardiac responses elicited by hydralazine (10). Thus, the increase in systolic pressure may be the result of a direct chronotropic and/or inotropic action. The fact that this does not occur in the angiotensin-induced hypertensive dogs may be due to the fact that: (a) the systolic BP level is close to its ceiling, or (b) that in some manner angiotensin antagonizes the effects of hydralazine upon the myocardium, either directly or indirectly.

A variety of blood pressure responses elicited by angiotensin in laboratory animals have been described by Peart (11). Tachyphylaxis is a frequent observation, which appears to be dependent on the particular octapeptide analogue of angiotensin employed (12). However, a continuous iv infusion of a small amount of angiotensin II failed to produce tachyphylaxis.

In addition, there are two dose-related responses accompanying continuous infusion. Low doses apparently produce a sustained pressor response for long periods (months), and higher doses produce a transient elevation in blood pressure which returns to control levels even though the infusion is maintained (13–15). This dose relationship also seems to be manifest on isolated cardiac tissue since Beaulnes (16), using cat papillary muscle and the atria of cat and rabbit, reported positive chronotropic and inotropic responses to concentrations of angiotensin less than 0.1 μg/ml, but above that, depression occurred.

Initially, investigators were led to the conclusion that sustained elevation of blood pressure in animals could not be obtained by angiotensin infusion (17). However, this study confirms the suggestion that a continuous iv infusion of a small amount of angiotensin II has the ability to raise blood pressure and maintain this elevated level. Although too few antihypertensive agents were employed, the data suggest that it may be feasible to utilize the acute angiotensin-induced hypertensive dog as a model for the pharmacological assessment of potential antihypertensive drugs.

Summary. Marked and sustained elevation of systolic and diastolic blood pressure results from the continuous iv infusion of angiotensin II in anesthetized dogs.

The administration of hydralazine, sodium nitrite, and hexamethonium (10 mg/kg,

iv) produced a fall in blood pressure in angiotensin-induced hypertensive dogs. However, hydralazine failed to produce a hypotensive response in normotensive dogs. This suggests the possibility that antihypertensive drugs may be evaluated in dogs made acutely hypertensive by angiotensin II infusion.

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