Failure to Replenish Catecholamine Stores in Reserpinized Dogs

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THE PURPOSE of this paper is to describe attempts at restoring the reserpinized animal's homeostatic mechanism and reversing the physiological alterations brought about by this drug. Such a procedure, if practicable, would have important clinical usefulness in anesthesia.

A simple clinical screening test for evaluating a patient's ability to react favorably to operation and anesthesia has been described.[1] This test is known as the Ephedrine Response Test (E.R.T.) The E.R.T. consists of monitoring the changes in pulse rate and arterial pressure obtained after the intravenous administration of 15 mg. of ephedrine sulfate. The test is recorded as *positive* if there is an increase in the pulse rate of 10 beats/minute and an increase in the systolic pressure of 20 mm. of mercury. The test is recorded as *negative* if the increase in pulse rate and pressure does not obtain or is less than the stated values. Greater reliance is placed on increase in the systolic pressure than upon increase in pulse rate. A systolic rise with an unchanged pulse is recorded as *positive*. This test was the basis for evaluating the adrenergic response in the experiments reported here.

Methods

Twenty mongrel dogs on a standard diet, weighing from 9.5 to 19 kg., were studied. Each dog served as its own control for the three phases of the experiment. Arterial blood pressure and lead 2 of the electrocardiogram were recorded on an Offner Type R Dynograph with direct ink writer. Femoral arterial pressures were measured by a percutaneous Cournand needle and a Statham P-23Db pressure transducer.

Anesthesia was induced and maintained with successive doses of 2.5 per cent thiopental sodium given through a slow intravenous infusion of 5 per cent dextrose in water. The lungs were hyperventilated through a cuffed endotracheal tube by mean of a Harvard respirator.

After preliminary investigation of the dose–response to ephedrine and comparison with the adrenergic effect produced by bilateral carotid artery occlusion, ephedrine was selected as an adrenergic challenge to determine the status of the norepinephrine stores.

Base-line pulse rate and arterial pressure were established and the response to a single intravenous injection of 0.2 mg./kg. of ephedrine sulfate measured. Catecholamine depletion was then produced by intramuscular doses of reserpine of 0.1 mg./kg. daily for three days. The E.R.T. was then performed at one day intervals until replenishment occurred as judged by the response to ephedrine. Following a two week interval, a base line E.R.T. was again obtained and the dogs were reserpinized.

The second and third phases of the experiment consisted of attempts to replenish the depleted catecholamine stores. Intravenous infusions of norepinephrine and dopamine were given to each of twenty reserpinized animals. After observing the individual response to ephedrine 0.2 mg./kg., an intravenous infusion of 1 mg. of norepinephrine was administered. The rate of infusion was determined by limiting systolic peak pressures to 300 mm. of mercury. The E.R.T. was performed after arterial pressures had returned to pre-infusion levels, and at 1- and 2-hour intervals after the initial post-infusion E.R.T. The E.R.T. was then performed at 24-hour intervals until replenishment occurred as judged by the response to ephedrine. After

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a two week interval, a similar technique was used in the administration of dopamine. A total dose of 10 mg. of dopamine was administered. With norepinephrine and dopamine, a stable plateau of pressure could be obtained at given rates of infusion, but this would fade upon decrease or cessation of infusion. Thus the time taken to recover the ephedrine response in each of twenty reserpinized dogs with and without dopamine and norepinephrine infusions was compared.

Results

Cathecholamine depletion by reserpine (0.1 mg./kg. intramuscularly daily for 3 days) produced a significant reduction in pulse rate and arterial pressure as shown in table 1 ($P < 0.05$).

The intravenous administration of reserpine in a single dose of 0.1 mg./kg. produced, after a latent period of approximately several minutes, a dramatic rise in blood pressure reaching peaks of over 300 mm. of mercury. There was evidence of increased ventricular irritability with runs of bigeminy as demonstrated by ECG. This effect was seen in the non-reserpinized dog and could be duplicated by doses of epinephrine or norepinephrine in the order of 0.5 mg. in a single intravenous injection. This phenomenon is best described as "depot dumping." Because of the severity of the response, this method of attempting rapid reserpinization was not used.

The doses of thiopental required for anesthetization of the reserpinized dogs was 25–50 per cent of that required for the non-reserpinized animal.

The non-reserpinized dog under light thiopental anesthesia showed a mean increase in systolic pressure of 37 mm. of mercury (range: 25–54 mm.) following intravenous ephedrine sulfate 0.2 mg./kg. This response was diminished after pre-treatment with reserpine to a mean of 3.5 mm. of mercury (range: 0–9 mm).

A mean time of 9.3 days (range: 7–12 days) was required to regain the response to ephedrine following reserpinization (fig. 1).

A mean time of 13 days (range: 8–16 days) was required to regain the response to ephedrine if the reserpinized dog were given an infusion of 10 mg. of dopamine (fig. 2).

A mean time of 11.9 days (range: 8–16 days) was required to regain the response to ephedrine if the reserpinized dog were given an infusion of 1 mg. of norepinephrine (fig. 3). Thus intravenous infusions of dopamine 10 mg. or norepinephrine 1 mg. in the reserpinized dog did not decrease the time required for recovery of a positive E.R.T.

Following cessation of norepinephrine or dopamine infusion, the arterial pressure returned to the reserpinized hypotensive level within a mean time of 15 minutes (range: 11–18 minutes) after norepinephrine, and 12 minutes (range: 8–15 minutes) after dopamine.

A false negative E.R.T. may occur as a result of reflex baroreceptor influence. This is blocked by preliminary medication with atropine sulfate (0.3 mg. intravenously).

Discussion

In recent years, hypotension associated with bradycardia has been reported in anesthetized patients who previously had received Rauwolfia alkaloids such as reserpine.[2] Reserpine has been shown to deplete catecholamine stores from the hypothalamus centrally and peripherally from postganglionic sympathetic nerve endings. The catecholamine content of the myocardium, arterial wall, adrenal medulla and brain is greatly diminished.[3] As a result of this depletion of norepinephrine from the postganglionic sympathetic nerve endings, the

TABLE 1. Catecholamine Depletion by Reserpine (0.1 mg./kg. for 3 days)

	Pre-treatment	Reserpinized
Pulse rate/minute	134 (Range: 66–192)	62 (Range: 36–95)
Blood pressure (mm. Hg)	125 Mean (Range: 85/45–220/160)	88 Mean (Range: 95/45–145/67)

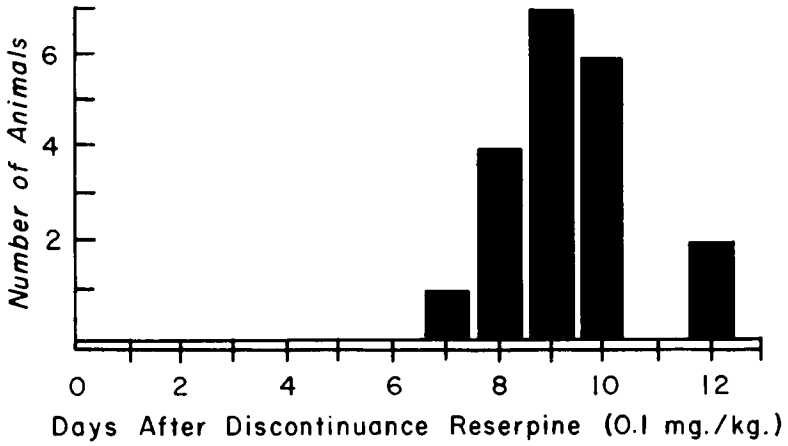

FIG. 1. Control—Catecholamine replenishment time measured by ephedrine response test (E.R.T.).

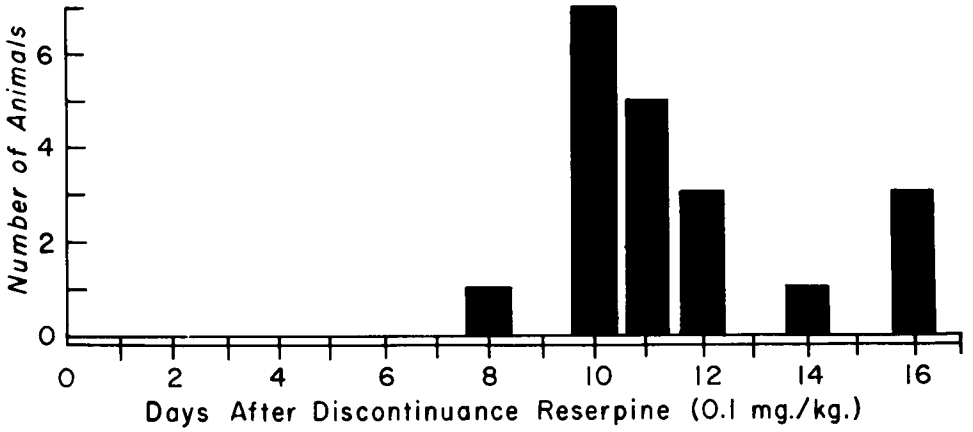

FIG. 2. Replenishment by exogenous immediate precursor-dopamine (10 mg. total infused). Catecholamine replenishment time measured by E.R.T.

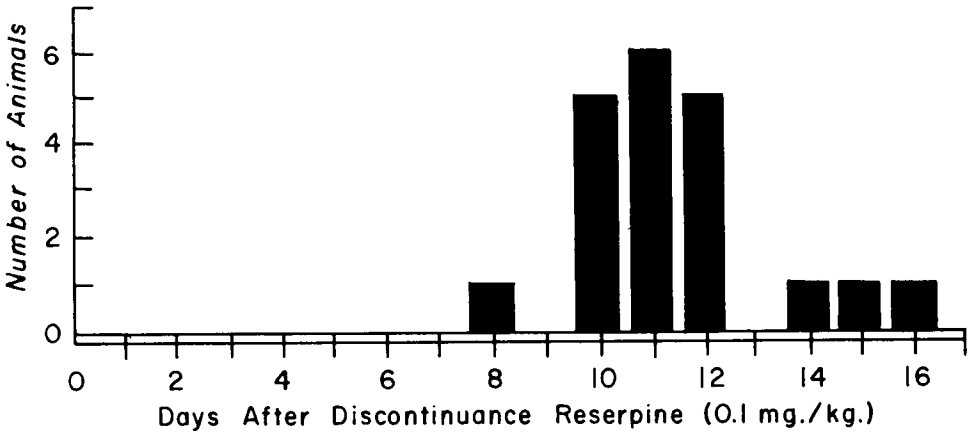

FIG. 3. Replenishment by exogenous norepinephrine (1 mg. total infused). Catecholamine replenishment time measured by E.R.T.

adrenergic effects of these nerves on the myocardium, cardiac conduction system and peripheral vascular bed are greatly diminished, or abolished. This alteration of the adrenergic mechanism impairs the compensatory adjustments required to maintain circulatory homeostasis during anesthesia.

Epinephrine, norepinephrine and phenylephrine have been shown to retain their effectiveness as vasopressors in the reserpinized dog.[4] However, their is a marked diminution in the response to ephedrine in the same preparation.

Burn and Rand have attributed the action of ephedrine to release of norepinephrine from postganglionic sympathetic nerve endings at the neuro-effector site.[5] Thus, following depletion of norepinephrine stores by reserpine, there should be a diminished response to ephedrine. Owing to this action as a releaser of norepinephrine, ephedrine was used to determine the status of the norepinephrine stores in the reserpinized dog. This Ephedrine Response Test (E.R.T.) is applicable to patients given the Rauwolfia group of drugs either alone or in combination with other antihypertensive agents. The test is based on the specific pharmacological effects of Rauwolfia alkaloids and ephedrine sulfate and is not useful for the phenothiazine group of tranquilizers. Like any test, it is not claimed to be 100 per cent reliable. Used to reinforce the anesthesiologist's, internist's or surgeon's clinical impressions, it may be of considerable aid.

Reserpine is detectable in the body in significant amounts for only a few hours, but the pharmacological effects persist for about two weeks. The possibility comes to mind of speeding up the return to normal adrenergic function by supplying exogenous norepinephrine or, secondarily, the immediate biological precursor, dopamine, in the hope of rapidly replenishing the norepinephrine stores. These studies demonstrated that the exogenous supply of the preformed hormone, norepinephrine, or its immediate biological precursor, dopamine, does not decrease the time required for biosynthesis and replenishment of the norepinephrine stores following reserpine induced depletion. Thus, it is postulated that reserpine not only causes the release of norepinephrine but also impairs the capacity of tissue cells to store norepinephrine. The tissues are rendered incapable of taking up exogenous norepinephrine, and replenishment must depend on biosynthesis and restoration of the adrenergic storage mechanism. The initial release of norepinephrine from the postganglionic sympathetic nerve by reserpine is virtually complete, and because of the slow rate of biosynthesis and restoration of the adrenergic storage mechanism, the result may be regarded as depletion.

Summary and Conclusions

Owing to its action as a releaser of norepinephrine, ephedrine sulfate was used to measure adrenergic responses. The adrenergic challenge provided by the "Ephedrine Response Test" proved effective in determining the status of the norepinephrine stores. A false negative Ephedrine Response Test (E.R.T.) may occur as a result of reflex baroreceptor influence: this was blocked by preliminary medication with atropine sulfate (0.3 mg. intravenously).

Reserpine not only releases stored norepinephrine but impairs the storage mechanism. The exogenous supply of norepinephrine or its precursor dopamine does not decrease the time required for sustained replenishment of adrenergic stores following depletion by reserpine. The duration of depletion is dependent upon the rate of biosynthesis of catecholamines and the restoration of the adrenergic storage mechanism. Used in proper perspective to reinforce the clinical impression, the "Ephedrine Response Test" may be of considerable clinical value.

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