THE EFFECT OF RESERPINE ON THE ACTION OF VARIOUS VASOPRESSORS

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HYPOTENSION has been reported in anesthetized patients who previously had been receiving reserpine. The fall in blood pressure did not respond satisfactorily to vasopressor drugs such as phenylephrine but was reversed by vagal blocking agents such as atropine or oxyphenonium.[1] Hypotension associated with bradycardia has also been reported in dogs anesthetized with a barbiturate and who had previously received reserpine.[2] The following experiment was undertaken to test the effect of the prior administration of reserpine on the action of commonly used vasopressors, to see if any of these decreased in effectiveness following reserpine.

METHODS

Epinephrine, norepinephrine, phenylephrine, methoxamine, mephentermine, ephedrine, and methamphetamine were tested as described below.

Mongrel dogs weighing from 11 to 17 kg. were anesthetized with pentobarbital (20 to 35 mg. per kg.). Each dog's trachea was then intubated with a cuffed endotracheal tube and the cuff inflated. The animals lungs were hyperventilated throughout the experiment with either an Emerson or a Harvard respirator. The femoral artery was cannulated with a polyethylene catheter and the catheter passed into the abdominal aorta. The catheter was connected to a U-type mercury manometer and the damped pressure thus obtained was read at appropriate intervals as a single, average figure. A needle was inserted intravenously, and a slow constant drip of 5 per cent dextrose in water was allowed to run throughout the experiment. The arterial blood pressure was allowed to stabilize (not vary more than 5 mm. of mercury pressure) for at least 10 minutes before an injection of vasopressor. A period of 45 or more minutes elapsed between each injection except in the case of epinephrine or norepinephrine where a minimum of 20 minutes was allowed. If during the course of the experiment the animal began to move or to shiver (and only in these cases) an additional 50 to 100 mg. of pentobarbital were given intravenously, following which a period of at least 20, and usually 30 minutes elapsed before the next injection of vasopressor was made. Drugs were injected intravenously through a 3-way stopcock connected directly to the intravenous needle and were immediately followed in each case by 5 ml. of normal saline.

In each experiment the dog was prepared as above, the effect of particular vasopressors upon arterial blood pressure observed and the animal allowed to recover. After a minimum of 5 days had passed, the animal was given a predetermined amount of reserpine intravenously. Eighteen to 24 hours following this, the procedure which had been performed previously on this dog was repeated. Care was taken to make the two procedures as nearly identical as possible: the same respirator was used at the same settings, identical vasopressors both in quantity and sequence were used, and in many cases the same artery was cannulated. However, a lesser amount of pentobarbital was generally found to be necessary to prevent shivering or movement.

By varying the quantity of reserpine from 0.1 mg. to 2.0 mg. per kg. in several dogs, it was found that a minimum of 0.4 mg./kg. was necessary to achieve alteration in response to intravenous injection of the vasopressors listed above. This amount (0.4 mg./kg. of reserpine) was used in the two experiments described below.

In the first experiment 3 dogs were used and vasopressors in the following sequence were tested: epinephrine .0002 mg./kg., phenylephrine 0.007–0.01 mg./kg., ephedrine 0.5 mg./kg., phenylephrine 0.007–0.01 mg./kg., methamphetamine 0.1–0.125 mg./kg., and phenylephrine 0.007–0.01 mg./kg. The dose

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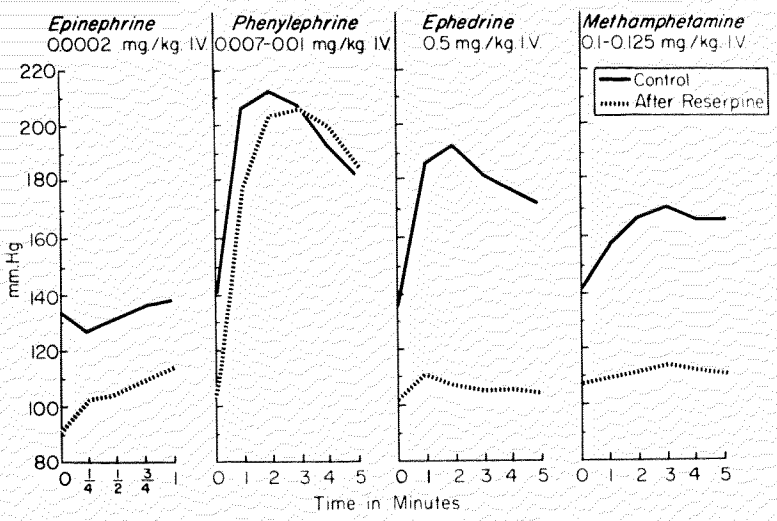

FIG. 1. Arterial blood pressure response to vasopressor drugs in dogs before and after reserpine administration. (First experiment.)

of each vasopressor might vary as indicated between each dog, but the dose given any one dog was not changed.

In the second experiment three dogs were used and the following vasopressors were tested: norepinephrine 0.001 mg./kg., methoxamine 0.125 mg./kg., methamphetamine 0.125 mg./kg., and mephenteramine 0.25 mg./kg. Norepinephrine was always given first. The sequence of administration of the other three drugs varied in each of the dogs.

RESULTS

Figure 1 shows the average alteration in response to the vasopressors tested in the first experiment. Except in the case of epinephrine and norepinephrine the 5 minutes following the injection of the vasopressor was selected to illustrate the effect because peak response could always be found in this period. For epinephrine and norepinephrine 1–1½ minutes sufficed for this purpose. From figure 1 it can be seen that the vasopressor effect of epinephrine and of phenylephrine is enhanced by prior administration of reserpine while under the same circumstances, vasopressor effect of ephedrine and of methamphetamine is decidedly depressed.

In at least one sense this may be an unfair comparison. Since arterial blood pressure is theoretically a product of cardiac output and peripheral resistance then an increase in either of the last two factors following the injection of a vasopressor will result in a *proportional* increase in the arterial pressure. Thus at different baseline blood pressures, *quantitative* increases might be different but proportional difference the same (or vice versa). It might be better then to represent changes by comparing the percentage (proportion) that

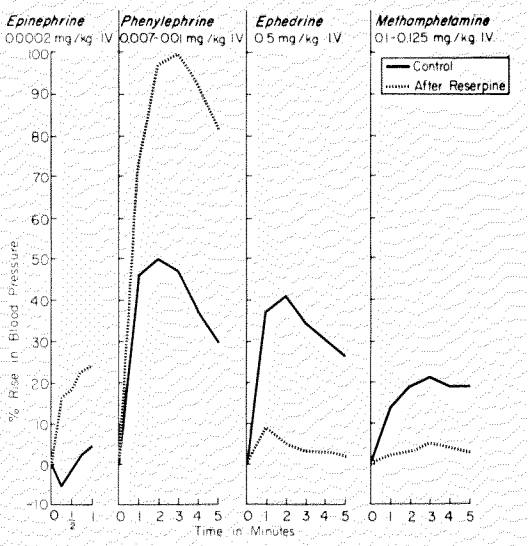

FIG. 2. Percentage alteration in arterial blood pressure produced by vasopressors before and after reserpine administration. (First experiment.)

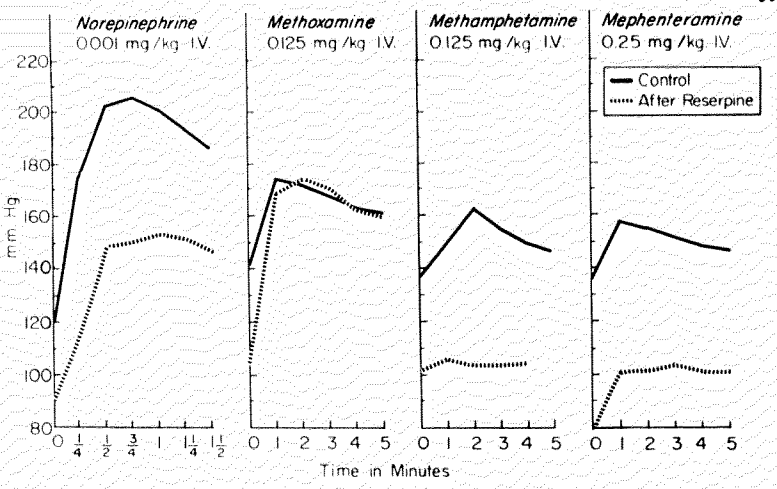

FIG. 3. Arterial blood pressure response to vasopressor drugs in dogs before and after reserpine administration. (Second experiment.)

the blood pressure rises from baseline pressure obtained immediately before the administration of the vasopressor. This is illustrated in figure 2. The effect here appears to be quite similar to that seen in figure 1.

Figure 3 represents the alteration in response to the various vasopressors tested in the second experiment. The effect of norepinephrine appears to be unchanged while that of methoxamine appears to be enhanced. Again the pressor action of methamphetamine is depressed as is that of mephentermine, although the latter to a lesser extent. Figure 4 shows the alteration in percentage rise. The changes noted in figure 3 remain essentially the same.

If the rises obtained in figures 1 through 4 are averaged they may be represented as in table 1. Again it can be seen that ephedrine,

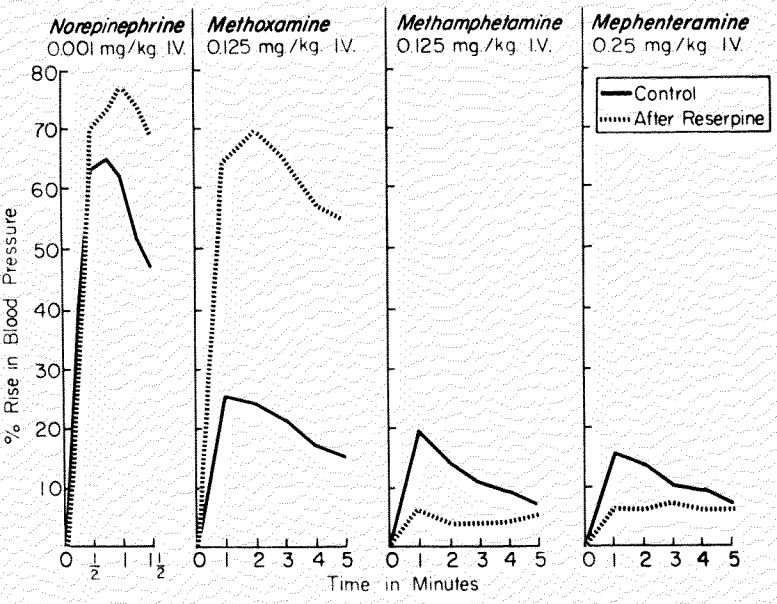

FIG. 4. Percentage alteration in arterial blood pressure produced by vasopressors before and after reserpine administration. (Second experiment.)

TABLE 1

BLOOD PRESSURE RESPONSE TO VASOPRESSORS BEFORE AND AFTER RESERPINE

Drug (mg./kg.)	Time Period Covered (minutes)	Average Pressure Rise Before Reserpine (mm. Hg)	Average Pressure Rise After Reserpine (mm. Hg)	Per Cent Average Pressure Rise Before Reserpine	Per Cent Average Pressure Rise After Reserpine
Epinephrine .0002	1	−0.5	18	−0	20
Morepinephrine .001	1½	64	53	54	65
Phenylephrine .007–.0.01	5	59	91	42	88
Methoxamine .125	5	27	60	21	62
Mephentermine .25	5	15	6	11	6
Methamphetamine part 2 0.1–.125	5	26	3	19	3
Methamphetamine part 3 .125	5	16	4	12	4
Ephedrine 0.5	5	46	4	34	4

methamphetamine, and to a lesser extent mephentermine are adversely affected in terms of their pressor actions by the prior administration of reserpine, while epinephrine, norepinephrine, methoxamine, and phenylephrine remain effective or increase in effectiveness.

DISCUSSION

The above findings may be clinically useful in the treatment of hypotension appearing in patients under anesthesia who have been on reserpine therapy. Recent work has shown that the administration of reserpine is followed by the disappearance from all tissues thus far investigated (brain, blood, heart, spleen, and adrenals) of all but a minor fraction of catechol amines.[3] Although the cause of hypotension in anesthetized patients who previously have received reserpine is not definitely known, one possibility in the light of the effect of reserpine on tissue epinephrine and norepinephrine might be stated thus: The response of the body to depression of blood pressure is dependent at least in part on the release of epinephrine and norepinephrine. In the patient on reserpine therapy the response to such depression of blood pressure (caused by anesthesia) may be impossible because of the scarcity of these amines. Lack of epinephrine would also help explain the bradycardia seen. Correction of the hypotension, then, might logically be done by supplying the necessary amount of the missing catechol amines or some appropriate substitute. It must be emphasized however that this study was done in dogs. The possibility of a different effect in humans should be considered.

Why one vasopressor remains effective or increases in effectiveness while another is decreased in effectiveness following reserpine administration remains uncertain. Speculation on the relation between amine oxidase inhibiting properties of ephedrine and methamphetamine (and mephentermine?) [4, 5, 6] or other enzyme inhibiting properties and their consequent impotency following reserpine injection cannot be supported or denied by the above experiment.

Since preparing our earlier report,[7] there has appeared an extensive report by Burn and Rand.[8] The results of their investigation are similar to ours. They suggest that the group of sympathomimetic amines which lose their effect following reserpine administration normally act by releasing noradrenalin or adrenalin from the store in the artery wall.

SUMMARY

Epinephrine, norepinephrine, phenylephrine and methoxamine were found to remain effective as vasopressors following reserpine administration. However, the prior administration of reserpine was followed by a decreased vasopressor action with ephedrine, methamphetamine, and mephentermine. This was tested in dogs, each animal serving as his own control. Clinical applications of the above data are suggested.

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SUBARACHNOID COMPLICATIONS Following 6,489 subarachnoid block anesthesias for private patients, five fatalities occurred for an incidence of 0.077 per cent (1:1,298). Three of these died on the operating table, one died of meningitis 24 hours after the operation and one expired within an hour after surgery. No fatalities occurred during the last 12 years. Four non-fatal major complications took place for an incidence of 0.061 per cent (1:1,621). They were one case each of arachnoiditis with permanent disability, transient meningitis, permanent paresthesias and footdrop. The technique employed was the same initiated 29 years ago except for minor variations. Surgery included procedures of the upper abdomen as well as those of the lower abdomen, perineum and lower extremities. It is believed that subarachnoid block is the safest of all anesthetic procedures except regional techniques. (*Morton, C. B.: Subarachnoid Block Anesthesia: A Twenty-nine Year Experience, Ann. Surg. 149: 617 (May) 1959.*)

JEHOVAH'S WITNESSES A case of cancer of the transverse colon with hemorrhage in a patient who was a Jehovah's Witness was presented. His bowel and stomach were resected. Postoperatively, his hemoglobin fell to 2.4 grams per cent. The medical, moral, and legal aspects of the problem of transfusion in Jehovah's Witnesses pose perplexing and probably insoluble problems. These are discussed by authorities in their respective fields. (*Fitts, W. T., Jr., and Orloff, M. J.: Blood Transfusion and Jehovah's Witnesses, Surg. Gynec. & Obst. 108: 502 (April) 1959.*)