Interrelationship of Drugs Influencing Arterial Pressure in Man

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Comparison of hemodynamic changes (cardiac output, renal plasma flow, and extremity blood flow) observed during reserpine-induced hypotension with those occurring during pentolinium-induced hypotension suggests better adaptation following reserpine. This difference is believed to be related to the gradation of onset of hypotension. It was found that reserpine-induced hypotension is potentiated by norepinephrine, and pentolinium-induced hypotension by serotonin. Pretreatment with the hypotensive agent increased the pressor response to norepinephrine and serotonin respectively, if the pressor substance was administered before the onset of hypotension.

The mechanism of action of pressor and depressor substances and their interrelationship have been of considerable interest to all workers concerned with the study of hypertensive disease. In this paper some studies are reported concerning relationships between reserpine (Serpasil), pentolinium (Ansolysen), norepinephrine, and serotonin. First, responses to 2 different hypotensive agents, namely pentolinium tartrate (Ansolysen) and reserpine (Serpasil) were compared with each other and correlated with the clinical behavior of the subjects in whom hypotension was induced. Then pressure responses to serotonin were studied. Finally, the behavior of pressure responses to norepinephrine and serotonin were ascertained after pretreatment with each of the 2 hypertensive agents, pentolinium and reserpine, before and after the hypotensive effect had become manifest.

Methods and Material

The response of hypertensive and normotensive subjects was studied in 74 experiments. Physiologic measurements of peripheral vascular beds were done by venous occlusion plethysmography, by means of apparatus previously described. Plasma flow through a visceral (renal) vascular bed was measured with the para-aminophipurate infusion method. Cardiac output was estimated from an arterial dilution curve after rapid injection of NaCl by the method described by Powers, with minor modifications. Whenever these measurements were carried out, the subject was tested under basal conditions in a constant temperature room at 20 C. and 55 per cent humidity, as described previously. Whenever only the responses of arterial pressure, heart rate, and clinical behavior were ascertained, the experiments were performed under ward conditions. Three drugs were given in single intravenous doses: reserpine (Serpasil) 3 mg., pentolinium (Ansolysen) 3.5 mg., serotonin 2.5 mg. Norepinephrine was used in a solution of 4 mg. in 1000 ml. of 5 per cent glucose in water at an infusion rate of 20 drops per minute.

Results

Single intravenous injections of 3.0 mg. of reserpine were given to 17 patients with essential hypertension in 38 experiments. In 36 of these, there was a marked drop in both systolic and diastolic pressures. The drop took place in a characteristic gradual fashion, reaching a maximum after 1 1/2 to 5 hours. The total duration of pressure response was from several hours to 5 days.

By contrast, after intravenous injection of a ganglonionic-blocking agent, in this case 3.5 mg.
mg. of pentolinium (11 experiments), there was an immediate drop in both systolic and diastolic pressures with return of diastolic pressure to pre-experimental levels within $\frac{1}{2}$ to 3 hours, while the return of systolic pressure required several hours.

The hypotensive response to reserpine was regularly associated with an early short-lasting increase in blood flow to the lower extremities, an equally brief but delayed increase in renal plasma flow, and no measurable change in cardiac output. The pulse rate remained unchanged or was slightly increased (fig. 1). In contrast is the hypotension following ganglionic blocking, which is associated with diminished cardiac output, a marked increase in blood flow to the extremities, and marked decrease in renal plasma flow. The known side effects associated with the precipitous fall in arterial pressure after administration of ganglionic-blocking agents are noticeably absent after reserpine. There was no postural hypotension or other clinical side effects, except mild flushing. Infusion of norepinephrine restored promptly the levels of both systolic and diastolic arterial pressure lowered by reserpine. When norepinephrine was infused after the hypotensive action of reserpine had set in (9 experiments) there was immediate rise in pressure. When the infusion was discontinued, pressures returned to the former hypotensive levels produced by reserpine and then dropped to even lower levels that were maintained for many hours (fig. 2).

Recently, attention has been focused on 5-hydroxy-tryptamine, commonly called serotonin. This substance, as Brodie and his co-workers\textsuperscript{5} have shown, has a peculiar relationship to reserpine. It is stored predominantly in intestines, brain, and platelets and, when released into the blood stream, it is rapidly destroyed by amine oxidase. Reserpine causes depletion of serotonin depots that outlasts the presence of reserpine in the serum. This point is of particular interest, because the hypotensive effect of a single dose of reserpine also outlasts the presence of the drug in the serum.\textsuperscript{6}

Serotonin, in doses of 2.5 mg., was administered intravenously in 14 experiments and was found regularly to increase both systolic and diastolic pressures. The rise was immediate (within 2 to 10 minutes) followed by a short-lasting drop in both levels of pressure (fig. 3). There was no essential change in response to the injection of serotonin during the maximal hypotension induced by intravenous injection of 3.0 mg. of reserpine in any of 7 experiments. When serotonin was injected 10 minutes after reserpine, however, before the onset of the hypotensive response, the blood pressure rose markedly, but the following hypotensive response to reserpine seemed unaltered.

In contrast, when 2.5 mg. of serotonin were injected during pentolinium-induced hypotension, there was a short elevation followed by a marked and sustained drop in both systolic and diastolic pressures exceeding considerably the hypotensive effect of pentolinium alone in all of 7 experiments (fig. 4). When 2.5 mg. of serotonin were injected immediately following 3.5 mg. of pentolinium,
there was a marked rise in arterial pressure followed by the expected hypotensive phase.

Studies carried out in normotensive subjects showed essentially the same directional responses as in hypertensives, but of considerably lesser magnitude.

**DISCUSSION**

During the hypotensive response to reserpine the pressor effects of norepinephrine remain unimpaired. The type of response in arterial pressure to intravenous administration of reserpine is distinctly different from that following ganglionic blockers. The paucity of changes in cardiac output and in blood flow through the visceral and peripheral beds studied, together with the absence of severe clinical side effects, suggests strongly that the slow decrease in arterial pressure following reserpine permits hemodynamic adaptation that may not be possible during the precipitous fall of pressure in response to ganglionic-blocking agents.

Epinephrine and norepinephrine have no effect upon pressure in the presence of adrenolytic agents or when adrenergic blockade has been achieved. However, when arterial pressure has been lowered by a ganglionic-blocking agent, the ability of epinephrine and norepinephrine to elevate pressures remains unimpaired. The same proved true in reserpine-induced hypotension. However, after discontinuation of norepinephrine infusion, the arterial pressure dropped to even lower levels than before. Even under these circumstances, the patients did not experience any distressing side effects, although they became sleepy and felt "weak."

There is some discrepancy in the reports on effects of serotonin upon arterial pressure in man. It has been described by various workers as hypertensive (Spies and Stone, dose: 0.5 to 5.0 mg.); hypotensive (Page and McCubbin, dose: 0.06 to 0.12 mg.); and biphasic (Page and McCubbin, dose: 0.3 to 1.8 mg.). Erspamer, who summarized the
findings, stated, "5-HT (serotonin) is neither a pure hypertensive nor a pure hypotensive agent. According to the dose, the route of administration, the anesthetic used, the neurogenic vascular tone, the general conditions of the cardiovascular apparatus and, above all, the animal species, 5-HT can elicit hypertensive, hypertensive and mixed responses." This statement refers to animal experiments as well as to those in man. The biphasic responses were described as a "fall, followed by a slight rise."

Hollander and Michelson and Wilkins reported that 0.3 to 1.5 mg. usually caused a hypertensive effect, with or without antecedent decrease in pressure. This effect was not prevented by hexamethonium, phentolamine (Regitine), atropine, and antihistaminic drugs.

In our experience serotonin in single intravenous doses of 2.5 mg. acts essentially as a pressor agent; usually this fast and fleeting action was followed by a slight but distinct depressor effect. This observation seems the more surprising, since it has been pointed out that "the levels of blood pressure in carcinoid patients are not consistent with the concept that serotonin is a pressor substance in man."

When serotonin was injected soon after reserpine, its pressor action seemed enhanced, but when it was given at maximal hypotension, its effect was the same as without reserpine. Pentolinium did not influence the pressor action of serotonin.

Serotonin did not exert any influence on reserpine-induced hypotension. When serotonin was given immediately following pentolinium, it did not influence the hypotensive effect, but when given at maximal hypotension, it markedly potentiated this phase. The observation is of interest that change in timing without change in dosage produces marked differences in the effects of depressor and pressor substances administered in sequence. It suggests that one is dealing, not simply with pharmacologic potentiation, but rather with alterations in pressure-regulating mechanisms.

**Summary**

Observations on the hemodynamic changes accompanying reserpine-induced hypotension are reported and compared with those associated with pentolinium-induced hypotension.
It is suggested that the gradual onset of hypotension following reserpine permits hemodynamic adaptation.

Norepinephrine, given at maximal reserpine-induced hypotension, and serotonin, given at maximal pentolinium-induced hypotension, appear to potentiate the hypertensive state markedly. When the pressor substances were given before the onset of hypotension, no such effect was observed, but there seemed to be an increased pressor response.

SUMMARIO IN INTERLINGUA
Observationes del alterationes; hemodynamic in hypotension inducite per reserpina es reportate e comparete con observationes correspondente in hypotension inducite per pentolinium. Es formulate le these quod le emergentia gradual del hypotension a reserpina permette un adaptation hemodynamic.

Le administration de norepinephrina in stato de hypotension maximal post reserpina e de serotonin in stato de hypotension maximal post pentolinium es apparentemente capace a potentiar le hypotensivitate a grados considerable. Quando le substantias pressori esseva administrate ante le declaration del stato hypotensive, nulle tal effecto esseva notate, sed il pareva occurrer un augmento del responsa pressori.

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