

# BLOOD PRESSURE CHANGES FOLLOWING COMBINED ADMINISTRATION OF VASOACTIVE DRUGS WITH SIMILAR EFFECTS

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UDC 615.225.015.4:612.143

**KEY WORDS:** systemic arterial pressure; pressor substances, depressor substances, combined administration

The main task in the regulation of the systemic hemodynamics is to maintain the blood pressure at an optimal level [4, 5]. Changes in this integral parameter under the influence of external and internal stimuli are the combined effect of simultaneously acting neurohumoral stimuli [3, 6]. Among the many factors involved in regulation of the hemodynamics an important place is occupied by biologically active substances [2, 5]. There is evidence of the pressor effects of one pair of vasoactive agents, namely noradrenalin and angiotensin, when administered simultaneously by intravenous infusion in chronic experiments on some rats and rabbits [7, 10, 11]. The authors cited demonstrated potentiation of the effects of these substances on blood pressure in the course of their combined administration over a long period of time. However, changes observed by other workers in the blood pressure during simultaneous stimulation of different reflexogenic zones are evidence of diminution of the combined effect compared with the theoretical sum of the effects of different stimuli. A response of this character was found during paired stimulation of the baroreceptors of the aortic arch and carotid sinus [8], receptors of the carotid sinus and atria [9], and also during a combination of pressor effects of simultaneous occlusion of the common carotid arteries and electrical stimulation of the median nerve [1]. The character of the response to paired stimuli for the cardiovascular system, having regard to the nonlinearity of its response, remained unclear.

The aim of this investigation was to study changes in systemic blood pressure (BP) during combined administration of a pair of vasoactive substances, causing similar changes in pressure of equal magnitude (noradrenalin and angiotensinamide, acetylcholine and histamine, isoproterenol and sodium nitroprusside).

## EXPERIMENTAL METHOD

Two series of acute experiments were conducted on 40 cats of both sexes weighing 3-5 kg, under urethane anesthesia (1 g/kg) with injection of heparin (1500 U/kg), with thoracotomy and artificial ventilation of the lungs. In the experiments of series I (19 cats) effects of intravenous injections of pressor agents — noradrenalin hydrotartrate (1-32  $\mu$ g/kg) and angiotensinamide (0.25-10  $\mu$ g/kg) — were investigated. Doses of the combination of substances which, separately, caused BP to rise by  $25 \pm 3$  and  $50 \pm 5\%$  relative to its initial level, specially determined in preliminary experiments, were used. In series II (21 cats) the fall of BP was studied in response to simultaneous administration of pairs of depressor agents: acetylcholine chloride (0.0001-10  $\mu$ g/kg), histamine dihydrochloride (0.25-8  $\mu$ g/kg), isoproterenol (0.25-16  $\mu$ g/kg), and sodium nitroprusside (0.5-5  $\mu$ g/kg). These substances were used in doses which, separately, caused BP to fall by  $15 \pm 2$  and  $30 \pm 3\%$  relative to its initial value, with the aid of specially determined dependences of the change in BP (effect) on intensity of action (dose). These vasoactive agents were diluted in physiological saline so that the test doses were contained in 0.5 ml of solution. The substances were injected into the animal's femoral vein in the course of 5-8 sec. BP was measured in the left subclavian artery by means of a pressure indicator with mechanotron transducer (made at the experimental workshops, Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR). Recordings were made on an N-327-5 high-speed automatic writer. The results were subjected to statistical analysis by the Fisher—Student *t* test.

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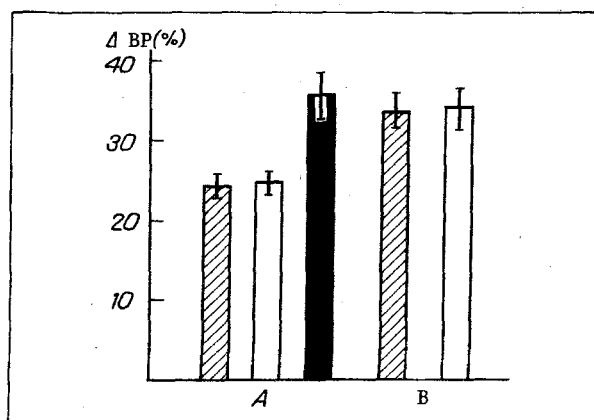


Fig. 1. Combined simultaneous intravenous injection of noradrenalin and angiotensinamide.

### EXPERIMENTAL RESULTS

Combined simultaneous intravenous injection of noradrenalin and angiotensin, in doses separately raising BP by  $25 \pm 3\%$  of its initial level, led to an increase of BP by  $37.4 \pm 3\%$  of its initial value (Fig. 1a). This value was close to the change in BP (Fig. 1b) observed on doubling the dose of noradrenalin ( $34.2 \pm 4\%$ ), and also of angiotensinamide ( $36.3 \pm 3\%$ ). Doubling the dose of the substance was used in experiments to study changes in BP in response to a combination of stimuli with equal effect and identical mechanism of action.

The effect of combined intravenous injection of noradrenalin and angiotensinamide using doses separately raising BP by  $50 \pm 5\%$  relative to its initial level was  $71.3 \pm 6\%$ . Comparison of this value with the pressor effects on BP of double the dose of each of the substances used ( $68.3 \pm 7\%$  for noradrenalin and  $63.2 \pm 6\%$  of the initial value for angiotensinamide), as in the previous case, demonstrated the absence of any significant differences between them.

Consequently, the experiments showed that combined simultaneous intravenous injection of two pressor agents, which when used separately lead to an equal rise of BP, leads to reduction of the combined effect relative to the potentially possible sum of the separate effects. Comparison of the rise of BP in response to combined injection of two agents, differing in their mechanism of action, with values of effects achieved by doubling the dose of each substance, shows that reduction of the combined pressor effect in the case of the action of paired stimuli is exhibited regardless of whether the rise of BP is brought about by the same or by different mechanisms.

To solve the problem of whether reduction of the combined effect of the pair of substances is specific only for the pressor agents tested, in the experiments of series II we used depressor vasoactive substances with different mechanisms of action on the cardiovascular system.

In response to combined simultaneous intravenous injection of histamine and acetylcholine in doses which, given separately, lower BP by  $15 \pm 2\%$ , the effect was  $21.9 \pm 3\%$  of the initial level (Fig. 2a). Their combined administration in doses separately lowering BP by  $30 \pm 3\%$  led to reduction of BP by  $44.7 \pm 4\%$  compared with the initial value. A combination of histamine and the adrenomimetic isoproterenol, in doses which, when injected intravenously separately, lower BP by  $15 \pm 2\%$ , caused BP to fall by  $21.8 \pm 2\%$  of its initial value (Fig. 2b), whereas combined injection in doses separately lowering BP by  $30 \pm 3\%$  led to a corresponding fall of  $45.3 \pm 4\%$  of its initial level.

These results are evidence of some special features of the BP changes in response to the combined action of two vasoactive drugs with similar effects (both pressor and depressor), namely reduction of the combined effect of a combination of stimuli relative to the potentially possible sum of the effects caused by their acting separately. However, this particular feature could depend on the mechanisms lying at the basis of action of the drugs.

To test this hypothesis, in seven experiments sodium nitroprusside, as a substance with direct myotropic action, was used as one of the depressor stimuli. When it was combined with histamine in doses which, separately, caused BP to fall by  $15 \pm 2\%$  of the initial level the combined effect amounted to  $20.9 \pm 3\%$  (Fig. 2c), whereas with combined intravenous injection in doses separately lowering BP by  $30 \pm 3\%$ , the combined effect amounted to  $44.1 \pm 4\%$  of the initial value. Consequently, reduction of

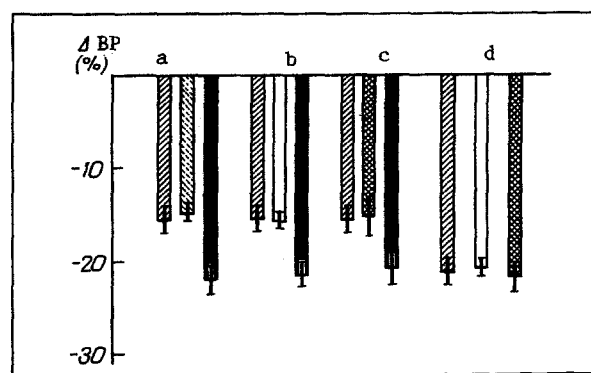


Fig. 2. Combined simultaneous intravenous injection of histamine and acetylcholine.

the combined effect on BP of a combination of stimuli relative to the potentially possible sum of the effects of the drugs acting separately, takes place irrespective of the mechanisms of action of the stimuli on the cardiovascular system.

The magnitudes of the effects of other possible paired combinations of depressor substances also point to reduction of the combined lowering of BP in the case of combined intravenous injection of the drugs relative to the sum of their separate effects. Comparison of the values obtained for the combined effects of combinations of vasoactive drugs with effects obtained by doubling the doses of each of the two agents separately (Fig. 2d) showed the absence of any significant differences between these values.

Thus when combinations of drugs, both pressor and depressor, with similar actions and equal effects, are used the combined effect on BP is smaller than the potentially possible sum of the effects of the same drugs acting separately. This decrease, as the experiments showed, is more marked in the case of combined action of depressor agents. On doubling the dose of each substance (combination of stimuli equal in effect and identical in mechanism of action) the combined effect on changes in BP also is reduced. This indicates that this effect is manifested independently of whether the same or different mechanisms lie at the basis of the changes in BP. Reduction of the combined effect of two stimuli compared with the potentially possible sum of their effects when acting separately, is probably a physiological feature distinguishing changes in BP in response to paired combinations of vasoactive stimuli similar in the direction and equal in the magnitude of their action.

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