

# PHARMACOLOGY

## CHANGES IN THE LEVEL OF THE ARTERIAL BLOOD PRESSURE IN DOGS DUE TO COMBINATIONS OF HYPOTENSIVE DRUGS

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In recent years the use of combinations of the hypotensive drugs instead of the individual preparations has become more widespread in the treatment of hypertension. The treatment of hypertension by such combinations enables a better therapeutic response to be obtained by doses smaller than those usually given of the individual components; in addition the side effects caused by the drugs are less marked. In the treatment of severe forms of hypertension in particular, a large series of combinations has been suggested, embracing drugs obtained from the root of Rauwolfia serpentina in conjunction with other drugs which lower the blood pressure. Freis [5], for instance, in all cases of severe hypertension, recommends the use of 3 mixtures containing, in different proportions, reserpine, pentaphyrrholidonium, apresoline and prostigmine. Finnerty [4] states that it is possible to obtain a better response by using small doses, and to reduce side effects by giving a combination of rauwiloid and veriloid. The same sort of effect was obtained by a combination of the preparations from Rauwolfia serpentina with hexamethonium and hydralazine [6] and so on. At the same time the search continues for new combinations of hypotensive drugs which, in small doses, would produce a prolonged fall in the arterial blood pressure without side effects.

The aim of the present investigation was to study the effect of a number of combinations of hypotensive drugs on the blood pressure of dogs in chronic experimental conditions.

### EXPERIMENTAL METHOD

Experiments were carried out on 7 dogs (5 males and 2 females) weighing from 8 to 25 kg. In two of them a persistent rise in the arterial pressure was produced by bilateral constriction of the renal arteries (the initial systolic pressure varied between limits of 140-190 mm of mercury and the diastolic between limits of 90-120 mm of mercury). In one old dog there was observed to be an increased arterial pressure presumably due to age (variations in the initial level of the systolic pressure between 130 and 158 mm of mercury and diastolic between 90 and 120 mm of mercury). In 4 dogs the arterial pressure was within normal limits (systolic pressure from 108 to 150 mm of mercury and diastolic from 68 to 90 mm of mercury).

As hypotensive drugs we used increpan (hypotonium) - a drug with a mainly peripheral action on the vessels, obtained by S. V. Andreev and his co-workers from the pancreas of cattle; gendon - a dutch preparation from the firm of Organon Holland, containing the total alkaloids of rauwolfia (main action on the vascular centers) and dibasol - a Soviet preparation, acting both directly on the smooth muscle of the vessel walls and on the central nervous system (S. V. Anichkov). We used the following combinations of the above-mentioned hypotensive drugs: gendon - increpan, gendon - dibasol and increpan - dibasol. All the drugs were given by mouth with minced meat every day for 10 days.

The blood pressure was measured by Korotkov's auscultatory method of the carotid artery which was brought near the surface in a muff of skin. The lowest arterial pressure before the experiment was taken conventionally to be the initial level.

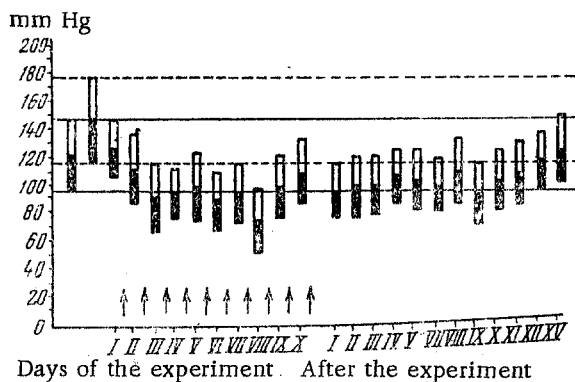


Fig. 1. Changes in the blood pressure in the dog Seryi with experimental renal hypertension in response to the combined oral administration of gendon and increpan for a period of 10 days. Gendon was given in a dose equivalent to 100  $\gamma$ /kg of rauwolfia alkaloids and increpan at the rate of 25 mg/kg daily.

Continuous horizontal lines – the lowest limits of variation of the initial systolic and diastolic pressure; the dotted lines are the highest limits of the same variations. The black-and-white columns show the results of serial measurements of the blood pressure in mm of mercury. Arrow – each single administration of the drugs. The blood pressure began to fall on the 2nd day of administration of the drugs. The maximum fall was observed on the 8th day (the systolic pressure fell by 48 mm and the diastolic by 44 mm of mercury). The blood pressure was restored on the 12th day after conclusion of the course of drugs.

20 to 100  $\gamma$ /kg of the rauwolfia alkaloids) and from 100 to 500 mg of increpan (from 8 to 25 mg/kg). The increpan was given 3 hours after the gendon.

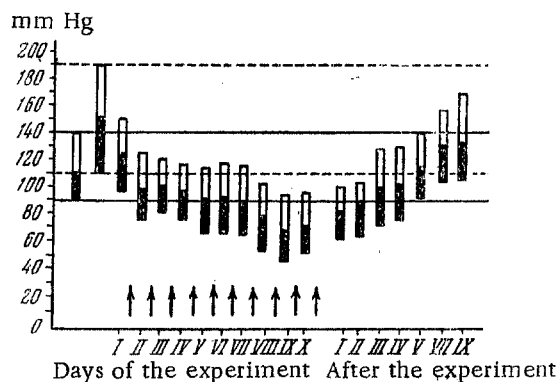


Fig. 2. Changes in the blood pressure of the dog Mishka with experimental renal hypertension under the influence of combined oral administration of gendon and dibasol for 10 days. Gendon was given in a dose of 100  $\gamma$ /kg of rauwiloid alkaloids, and dibasol in a dose of 2.5 mg/kg daily. Legend as in Fig. 1.

The arterial pressure began to fall on the 2nd day of the course of treatment. The maximum fall was on the 9th day of administration of the drugs (the systolic pressure fell by 44 mm and the diastolic by 40 mm of mercury). The blood pressure was restored on the 5th day after the conclusion of the course of treatment.

The combination gendon – increpan was given to 6 dogs: two with experimental renal hypertension and four with a normal blood pressure. The animals were given daily from  $\frac{1}{4}$  to 1 tablet of gendon\* (from

## EXPERIMENTAL RESULTS

In all the experiments an obvious fall of the systolic and diastolic pressures was observed, beginning on the 2nd-9th day of taking the drugs and continuing for 7-11 days after the conclusion of the course. The systolic pressure fell by 20-48 mm of mercury (by 18-32%) and the diastolic by 10-44 mm of mercury (by 14-44%) below the initial level depending on the dose of the preparations used in the combination (Fig. 1).

From results obtained previously, the blood pressure remained lowered after the dogs had finished feeding on increpan in those cases only when the drug was given in doses of 25 mg/kg for a longer time (30 days) or when the daily dose was increased to 50-100 mg/kg, i.e. when the dosage was from 2 to 12 times larger than that used in the present investigation.

Administration to a dog (with hypertension due to age) of gendon alone in a dose from 2 to 25 times greater than that used in the combination (2 tablets or 222  $\gamma$ /kg of alkaloids of rauwolfia daily), although it caused an obvious fall in the systolic (by 28 mm of mercury, or by 22%) and the diastolic pressure (by 22 mm of mercury, or by 24%), this fall was, however, not persistent. The blood pressure was restored on the 2nd day after feeding of this preparation ceased.

Feeding of dogs on a combination of gendon and increpan thus caused a more prolonged hypotensive effect than did the administration of each of the drugs separately, even in large doses.

\*Each tablet contains approximately 2 mg of rauwolfia alkaloids.

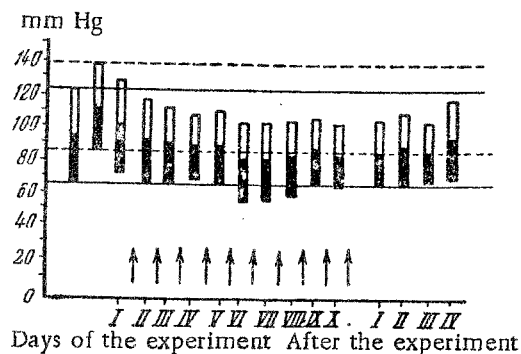


Fig. 3. Changes in the blood pressure of the dog Tsygan (normal blood pressure) under the influence of combined oral administration of increpan and dibasol for 10 days (dose of increpan 18 mg/kg, and of dibasol, 2 mg/kg, daily). Legend as in Fig. 1.

There was an insignificant fall in the systolic pressure. The diastolic pressure remained practically within the limits of the lower level of the initial pressure.

The arterial pressure was restored on the 5th day after the conclusion of the course of feeding with the drug (Fig. 2).

We observed the weakest hypotensive effect after administration of a combination of increpan and dibasol. This combination of drugs was given to 2 dogs with normal arterial pressure. The daily dose of increpan was 18 and 25 mg/kg, and of dibasol 2 and 3 mg/kg. In both experiments an insignificant fall (by 10 mm of mercury) was observed in the diastolic pressure. The systolic pressure was reduced only in the dog Tsygan (by 20 mm of mercury). In one dog the arterial pressure was soon restored, and in the other, on the 2nd day after the conclusion of the course of feeding with the drugs (Fig. 3).

In the Table are summarized the results of oral administration to dogs of various combinations of the hypotensive preparations.

In all the experiments in which gendon was given side effects were observed, shown in the form of drowsiness, weakening of motor activity, to the extent of a considerable degree of adynamia, disturbances of the gait, diarrhea, vomiting and refusal to eat. However, in half the experiments in which the combination of gendon and increpan was used, these manifestations were less severe. These side effects developed on the 4th-10th day of feeding and disappeared on the 4th-10th days after the conclusion of the course, depending on the degree of their severity. The administration of a combination of increpan and dibasol was not accompanied by any side effects.

It can be seen from the results of the experiments that the most prolonged hypotensive action was produced by the combination of the rauwolfia alkaloids with increpan.

In order to achieve a more prolonged fall in the blood pressure, much smaller doses of the drugs forming the combination were required than by the use of each drug separately. A reduction in the severity of the side effects was also observed (in half the experiments).

Oral administration of rauwolfia alkaloids (gendon) and dibasol to dogs was not accompanied by any perceptible increase in the hypotensive action of the rauwolfia alkaloids; nor was the degree of the side effects reduced.

Administration of increpan in combination with dibasol led to a reduction in the hypotensive action of increpan. Thus the simultaneous administration of the rauwolfia alkaloids and increpan evidently showed promise

Two dogs (with "age" and renal hypertension) received a combination of gendon and dibasol. Gendon was given in a dose of 1 tablet (100 and 111  $\gamma$ /kg of alkaloids) and dibasol at the rate of 50 mg (2.5 and 2.8 mg/kg) daily. The interval between the administration of gendon and dibasol was 3 hours.

In both experiments a considerable fall in the arterial pressure was observed, but with rapid restoration to its initial level after cessation of feeding. In the dog Mushka with hypertension due to age, the fall in the diastolic pressure was greater (by 32 mm of mercury, or by 35%) and the fall in the systolic pressure was slight (by 10 mm of mercury, or by 8%). Restoration of the normal value of the systolic pressure started even before the conclusion of the course of the drug — on the 10th day of feeding. The diastolic pressure was restored 3 days after the administration of the drug ceased. In the dog Mishka with renal hypertension, the systolic and diastolic pressures fell by almost the same amount: the systolic by 44 mm of mercury (by 31%), the diastolic by 40 mm of mercury (by 44%).

Changes in the Blood Pressure of Dogs in Chronic Experiments in Which Various Combinations of Hypotensive Drugs Were Administered

Serial No.	Sex	Weight, kg	Type of combination	Sessional dose per kg body weight	Initial blood pressure, mm of mercury		Maximum fall of blood pressure				Duration of fall after cessation of feeding of drugs, days
					systolic	diastolic	mm of mercury		%		
							systolic	diastolic	systolic	diastolic	
1	♂	20	Gendon - increpan	100 γ and 25 mg	150	100	48	44	32	44	11
2	♂	20	The same	100 γ and 25 mg	140	90	26	24	19	27	9
3	♀	25	" "	20 γ and 8 mg	110	70	20	20	18	28	9
4	♂	18	" "	28 γ and 11 mg	130	70	36	10	28	14	8
5	♂	8	" "	62 γ and 12 mg	108	68	24	22	22	32	7
6	♂	11	" "	45 γ and 9 mg	128	70	32	20	25	28	7
7	♂	20	Gendon - dibasol	100 γ and 2.5 mg	140	90	44	40	31	44	4
8	♀	18	The same	111 γ and 2.8 mg	130	90	10	32	8	35	3
9	♂	8	Increpan - dibasol	25 and 3 mg	108	68	0	10	0	15	1
10	♂	11	The same	18 and 2 mg	128	70	20	10	16	14	0

in the treatment of hypertension, especially in those cases when treatment by one preparation alone was ineffective. At the same time dibasol weakens the hypotensive action of increpan, a feature which must be remembered when the latter drug is used clinically.

The question of the search for more effective methods of combined administration of the rauwolfia alkaloids and increpan when the blood pressure is raised calls for further experimental study.

#### SUMMARY

The author studied the effect of the combination of the following hypotensive drugs on the blood pressure of dogs with normal blood pressure and with experimental hypertension: gendon-increpan, gendon-dibasol, increpan-dibasol. The preparations were given per os for 10 days. The blood pressure was measured in the carotid artery enclosed in a skin flap. The best hypotensive effect was obtained from the use of gendon-increpan combination (gendon was given in the dose of 20-100  $\gamma$ /kg of Rauwolfia serpentina alkaloids, increpan - 8 to 25 mg/kg). Systolic pressure was decreased by 18-32%, diastolic by 14-44%. The blood pressure was reestablished 7-11 days after the termination of the course of treatment. Each preparation used in combination gave a much lower effect than when used separately. Poor effect was obtained when feeding the dogs by the combination of gendon and dibasol. The use of the increpan-dibasol combination gave a lesser hypotensive effect than administration of increpan alone.

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\* In Russian.