

ON SOME PHARMACOLOGICAL PROPERTIES OF THE ALKALOIDS OF VINCA MAJOR

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Pharmacological studies of the alkaloids of *Vinca minor* and *Vinca herbaceae* revealed that compounds found in these plants are highly active pharmacologic agents. They have a sedative effect on the central nervous system, they considerably lower the blood pressure, they block some ganglia, belonging to the parasympathetic part of the vegetative nervous system and interrupt the transmission of nervous impulses in the myo-neural synapses, realizing a curare-like effect; they also anesthize the receptors of the cornea etc. On the basis of these investigations a market product was delivered under the name of Vincapan, containing the total alkaloids of *Vinca minor*, whose previous clinical trial seemed quite encouraging. All this stimulated the phytochemical and pharmacological elaboration of the third representative of the botanic family Apocynaceae. This plant also belongs to the species *Vinca* — *Vinca major*, grown in our country. Mention should also be made of the fact that according to phytochemical investigations of a number of foreign authors (7) *Vinca major* contains alkaloids with indolic structure, which are more or less structurally related to reserpine, whose polypharmacological activity and great therapeutic significance are well known.

These were the motives for our systematic pharmacological analysis of the total alkaloids of this plant, obtained at the Chair of Pharmacology at the Higher Medical Institute in Varna.

Some results of this study are reported here.

I. The effect of *Vinca major* alkaloids on the blood pressure of animals without narcosis.

After we were convinced that the alkaloids of *V. major* in an acute experiment on cats under urethan narcosis considerably and continuously lower blood pressure, we decided to prove this effect in the conditions of a chronic experiment on rabbits without narcosis. We used male animals weighing 2800—3200 g. Blood pressure was measured by means of a diaphanosopic mercury manometer at a precisely determined area of a. centralis auriculae. As the experiment with one animal continued for 3—4 hours and sometimes even more the determination of blood pressure was made in 2 animals at intervals of 30 minutes for 4 hours with a view to establish the range of variations of the utilized index in this method of investigation. As it is seen on Table 1 the blood pressure of rabbits measured on a. centralis auriculae proved to be relatively constant. Control examinations in control and in experimental animals pointed out that in our case it varied between 58 and 62 mm of mercury or 60 mm mercury on the average.

Table I

Measurement	62	60	62	58	59	60	48	59	59	61
mm mercury	I	II	III	IV	V	VI	VII	VIII	IX	X

The experimental animals after a twofold measurement of the blood pressure at an interval of 30 minutes received by intravenous route 0,005 per kg body weight alkaloids of *V. major* dissolved in distilled water. The following data graphically presented on Fig. 1 were attained in all experiments performed with the five experimental animals. From the figure it becomes evident that the injected alkaloids lower blood pressure for a mean duration of 3½ hours. In some cases this hypotensive effect

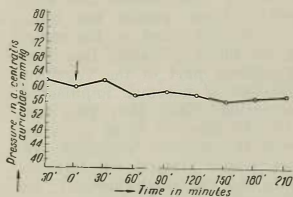


Fig. 1. a) Blood pressure measures in *a. centralis auriculae* on control animals (rabbits) for 3½ hours

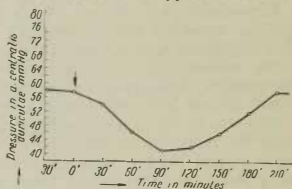


Fig. 1. b) Blood pressure, measured in *a. centralis auriculae* on animals (rabbits) after intravenous administration of 5 mg/kg body weight total alkaloids of *Vinca major*

lasted longer and in others it was shorter. Moreover, the maximal lowering of the blood pressure occurred one and a half hours after the administration of the alkaloids.

II. The effect of the alkaloids of *V. major* on the gastric, rectal, cutaneous and pulmonary temperature in rabbits.

In these experiments carried out with male rabbits weighing 2700 to 3500 g the temperature of the animals was measured at intervals of 30 minutes until recovery occurred after the administration of alkaloids by means of galvanometric thermometer RFT, supplied with a probe and a special end piece for temperature calibration in the stomach, rectum, the skin, and the expired air of the lungs. In order to estimate the normal variations of temperature in the various parts of the body (stomach, rectum, skin, and lungs) 10 measurements were performed for 3 hours in two animals without any administration of drugs. The alkaloids of *V. major* were intravenously administered in doses of 0,005 per kg body weight to the experimental animals after a threefold determination at 30 minutes intervals of various types of temperatures (data of this determination served as a comparative background). Temperature measurements were thereafter performed again at 30 minute intervals until the values of the indices returned to normal.

The results obtained indicated that in control animals as well as in control measurements in experimental animals before treatment with *Vinca* alkaloids the temperatures insignificantly vary and present the

following mean values — 40,1°C for the stomach, 39,9°C for the rectum, 35,2°C for the skin and 29,2°C for the lungs /See Table 2/.

The changes in the various types of temperature after intravenous administration of *V. major* alkaloids are also presented on Table 2.

Table 2

Temperature reading		Gastric temperature		Rectal temperature		Skin temperature		Pulmonary temperature	
		°C	Difference in °C	°C	Difference in °C	°C	Difference in °C	°C	Difference in °C
Before v. M.	Mean temperature	40,1	0,0	39,9	0,0	35,2	0,0	29,2	0,0
After injection of <i>V. M.</i> at 30 minutes intervals	I reading	40,3	+0,2	39,2	-0,7	32,8	-2,4	29,0	-0,2
	II "	40,3	+0,2	38,8	-1,1	30,7	-4,5	28,5	-0,7
	III "	40,4	+0,3	38,8	-1,1	30,5	-4,7	28,3	-0,9
	IV "	40,3	+0,2	38,4	-1,5	31,7	-3,5	30,0	+0,8
	V "	40,3	+0,2	40,0	+0,1	33,8	-1,4	29,5	+0,3
	VI "	40,1	+0,0	40,3	+0,4	34,5	-0,7	29,9	+0,7

Several facts make a definite impression. First, only of all the gastric and cutaneous temperatures show in all measurements following the administration of *Vinca major* identical changes which are however reciprocal: while cutaneous temperature is lowered, gastric temperature rises by 0,2—0,3°C. Moreover, to the maximal lowering of cutaneous temperature which occurs about an hour after the administration of alkaloids corresponds a maximal rise in gastric temperature. As far as the rectal and pulmonary temperatures are concerned the first three or four measurements after the administration of the alkaloids the temperature values decrease, whereas in the last measurements they are subjected to reverse changes — i.e. temperature is increased. The comparison of data concerning the effect of *Vinca major* on blood pressure of intact unanesthetized animals with these related to the existence of a certain parallelism in time — the maximal effect of the alkaloids in both cases takes place about an hour after their administration. At present it is difficult to state whether any dependence exists between these two phenomena which are parallel in time. Perhaps on the other hand the lowering of cutaneous temperature in his turn compensatorily increases the metabolic thermogenic processes, which leads to a mild elevation of gastric temperature. It seems that these thermogenic reactions compensate considerably later the lowering of temperature in the rectum and the lungs.

III. The effect of *Vinca major* alkaloids on the oxygen utilization by various tissues.

According to other personal unpublished data the alkaloids studied so far exert also a marked neurotropic effect. That is why we decided therefore to prove their effect on oxygen utilization by the brain. For comparison we investigated the effect of these substances also upon oxygen utilization by the tissues in the facial region, which as it is well known, are supplied by an arterial vessel common for the brain — a. carotis communis and which simultaneously with this differ radically as regards their function compared with it. Last but not least we studied the relation of *Vinca* alkaloids to oxygen utilization by the upper portion of the small intestines with regard to the fact that they similarly to the

brain represent a depot for 5-hydroxytryptamine (5HT) and if the eventual effect of the examined alkaloids on the consumption of oxygen by the brain is related to the effect upon the liberation of this monoamine from the brain depots and its subsequent transformations (oxydative deamination requiring additional quantities of oxygen) it may follow, that this effect would be directed to the small intestines as well.

The degree of oxygen utilization by the various tissues was determined after the arterial-venous difference in oxygen saturation of the hemoglobin in the arterial and venous vessels of the respective organ. By means of a combined oxyhemometer model 057 a production of "Krasnogvardeets" — Leningrad oxygen saturation of the hemoglobin was determined on blood samples of 0,4 ml each, taken at 30 minutes intervals from a. carotis communis, sinus sagitalis superior, vena jugularis externa, a. mesenterica cranialis and vena mesenterica cranialis. The experiments were performed on 20 cats. Two of the animals were not treated with the examined alkaloids. No change was established in them during the experiment which lasted several hours, in oxygen consumption in the examined three regions — the brain, facial tissues and the proximal segment of the small intestines. With a view to test the role

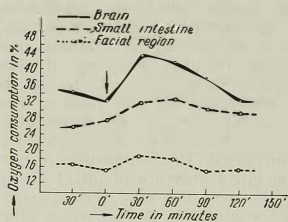


Fig. 2. Changes in oxygen consumption by the brain, the tissues of the facial region and the proximal segments of the small intestines of cats under the effect of the alkaloids of *Vinca major* (5 mg/kg body weight intravenously)

of narcosis for our studies we made use of ether and chloralosa narcosis in 6 animals, whereas in the remaining 14 we used urethane. It occurred that the effect of V. major alkaloids does not depend on the type of narcosis with regard to these studies. For that reason the results obtained are summed up for all animals irrespectively of the type of narcosis used during the experiment. They revealed that oxygen utilization in the examined three regions in control animals as well as in the experimental ones prior to alkaloid administration amounts to 34,0% for the brain, 16,1% for the facial tissues and 28,6% for the upper portion of the small intestines. Following administration of the alkaloids, oxygen blood levels tested in samples from a. carotis communis, a. mesenterica cranialis did not change, whereas in venous blood they decreased in varying degree depending on the organ from which the venous vessel collects blood. The most marked decrease of blood oxygen content involved the blood drained from the brain in sinus sagitalis superior. For the blood coming from the intestines and the facial region it was so mild that it may be included within the range of variations. In other words, as it is seen on Fig. 2 under the influence of the introduced alkaloids, the utilization of oxygen by cerebral tissue is markedly increased. For that reason its content in the blood which drains this organ diminishes. It should be regretted that data from the present studies do not render a

decision possible, which one of the theoretical possibilities is realized in this case.

Only the fact that with regard to the intestines the examined alkaloids exert almost no effect in the direction studied, gives us grounds to assume that this effect is not directly related to the period of observation with 5 HT and its metabolism in the organism. Nevertheless stress should be laid on the fact that these findings deserve serious attention, particularly as far as their clinical use is concerned.

Conclusions

The total alkaloids of *Vinca major*:

1) considerably and continuously (for several hours) reduce blood pressure not only under conditions of acute experiment, but also in intact animals, which are subjected to narcosis;

2) reduce cutaneous temperature by 4—5°C, to a much lesser extent rectal temperature, and exert almost no effect upon pulmonary temperature; they elevate however gastric temperature of experimental animals, though only to an insignificant degree;

3) increase oxygen consumption by cerebral tissues without exerting changes with regard to facial tissues and the proximal segments of the small intestines (in the basin of a. and v. mesenterica cranialis).

RÉFÉRENCES

1. Желязков, Д. К. — *Съвр. медиц.*, 9, 16, 1958. — 2. Бойчинов, А. Д. К. Желязков, Д. Панова. — *Фармация*, 6, 14, 1959. — 3. Панов, П. и кол.—*Докл. Болг. Ак. Наук*, 14, 139, 1961. — 4. Roussinoff, K. S. D. K. Jelyaskoff, V. P. Guergieff. — *Archivio Italiano di Science Pharmacol.*, v. XI, f. 2, 3, 5, 1961. — 5. Roussinoff, K., D. K. Zhelyaskov, V. Georgiev. *Compt. rend. de l'Acad. Bulg. des Sciences*, 15, 3, 329, 1962. — 6. Русинов, К., Д. Желязков — *Изв. на И-та по физиология при БАН*, т. V, 271, 1962.—7. Farnsworth, N. R., A. S. Fong, R. N. Blomster — *J. Pharmaceutical Sciences*, v. 51, 3, 217, 1962.

К ФАРМАКОЛОГИЧЕСКИХ СВОЙСТВАХ АЛКАЛОИДОВ VINCA MAJOR

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РЕЗЮМЕ

По данным авторов тотальные алкалоиды *Vinca major* понижают выражено и длительно кровяное давление у интактных животных без наркоза. Они повышают значительно использование кислорода мозговой тканью, не изменяя ее в тканях области лица и в области проксимальных отделов тонких кишок. Кроме этого, упомянутые алкалоиды понижают кожную температуру на 4—5°C, значительно слабее понижают температуру в прямой кишке, почти не оказывают влияния на температуру легких и очень слабо повышают температуру в желудке подопытных животных. Обсуждаются возможные механизмы получаемых эффектов.