

PHARMACOLOGY

THE ANTISHOCK EFFECT OF AMINAZINE AND MEPAZINE

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Artificial hibernation is now being used successfully in clinical prophylaxis and treatment of shock.

The main components in the mixtures which are used to achieve a state of hibernation are derivatives of the phenothiazine group of compounds. It is suggested that these compounds have the property of increasing the organism's resistance to trauma by lowering the intensity of metabolic processes. However, it is difficult to form an opinion of the strength of antishock effect of phenothiazine derivatives on the basis of clinical data only, since usually a whole complex of antishock measures is employed. Therefore, experimental investigations of the antishock effect of the compounds mentioned, tested against models of shock-like conditions, are of considerable interest. As shown by L. Beck and T. Redick [2], R. Milligan and E. F. Stohlman [5], preliminary administration of chlorpromazine lowers the percentage of white mice dying from tourniquet shock. Similar data were obtained by S. Courvoisier [4] who subjected white rats to traumatic shock.

The present work is devoted to the study of the antishock properties of mepazine — one of the new derivatives of the phenothiazine series, synthesized by S. V. Zhuravlev and collaborators at the Institute of Pharmacology and Chemotherapy, AMN SSSR. The antishock properties of aminazine were also studied for comparison.

The antishock properties of these preparations were compared with the similar effect of morphine as a substance used extensively in the prophylaxis and treatment of traumatic shock, both experimentally and clinically.

EXPERIMENTAL METHODS

The Noble and Collip [6] model of traumatic shock was used in the experiments but modified for white mice. The animals, with their limbs bound, were placed in a special drum 60 cm in diameter and 10 cm long. Within this drum two three-faceted projecting prisms were placed at diametrically opposite points on its circumference. The drum was rotated with the help of a synchronized electric motor with a speed of 30 rpm. During rotation the mice fell from one prism to the base of the other one which again lifted them upward from where they again fell to the opposite prism and so on. Not more than two animals were placed in the drum at the one time. As the result of these falls the mice developed a shock-like state and if rotation was continued they died.

According to the data available in the literature, the disturbances which arise in the animals as the result of such repeated falls within the drum resemble in many respects the disturbances observed in traumatic shock in man. Thus, R. Chambers and B. Zweifach [3] found that in the case of white rats 650-800 falls were followed by a drop of blood pressure to 30-40 mm Hg, the body temperature dropped from 96-100° Fahrenheit to 93-95°, the animals were extremely depressed, lay motionless, did not respond to pain stimuli, their skin showed pallor. Investigation of the capillary circulation showed that as the result of trauma there was engorgement of the intestinal blood vessels and constriction of the cutaneous ones. The total plasma volume dropped, as a rule, by 12-15% as compared with the initial level. The pathologic changes mentioned indicate that the described condition of the animals can be considered as a model of traumatic shock.

A total of 16 series of experiments has been carried out on 320 mice. The mice were subjected to "rotation" in the drum until they died; the number of falls after which each mouse died was recorded. The data obtained were used to plot a curve of dependence of death (in percentages) on the degree of trauma.

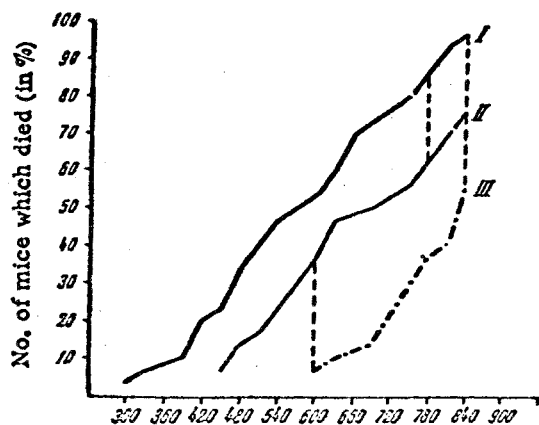


Fig. 1. Relation of death among mice and the degree of trauma in experiments with mepazine (II) and morphine (III), control (I).

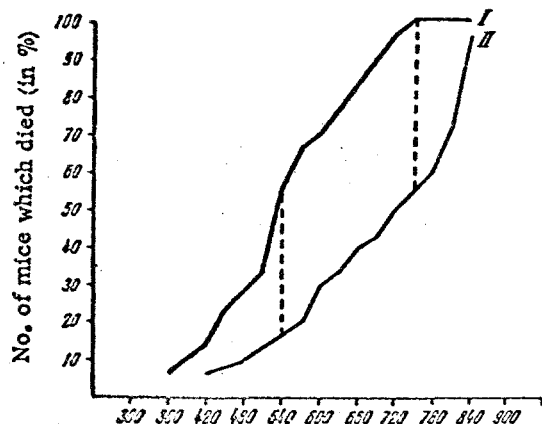


Fig. 2. Relation of death among mice and degree of trauma in experiments with aminazine (II), (I) control.

Control experiments showed that the relation of the animals' death to the degree of trauma was expressed by a fairly constant value and could be established even in experiments with relatively small numbers of mice.

Mepazine, aminazine and morphine were injected intraperitoneally 30 minutes prior to the infliction of trauma.

EXPERIMENTAL RESULTS

The experiments showed that mepazine and aminazine in the dose of 1 mg/kg body weight lowered the percentage of deaths among the mice. The most effective action of these preparations was observed when the trauma was of moderate degree (Fig. 1, 2). A similar relation between the antishock effect and the degree of trauma was also noted when other pharmacologic compounds were used [7].

The curves show that following administration of mepazine the number of mice which died from trauma of moderate degree dropped to 20%; it dropped by 45% when aminazine was given. Statistic treatment of the data obtained by the "chi-square" method showed that the difference between the mean results of the experiments and controls was significant.

Increasing the doses of mepazine and aminazine to 5-10 mg/kg did not raise survival among the mice - a reverse effect could even be observed. Similar data were obtained by Courvoisier in experiments with chlorpromazine on white rats [4]. Apparently the higher doses of these preparations lead to predominance of their toxic effect over their antishock properties.

Experiments with morphine gave results of a similar nature. When small doses of the preparation (1 mg/kg) were given the number of animals which died fell by 42% as compared with the control, but when higher doses were used the number increased rather than decreased. The greater effectiveness of small doses of morphine has also been noted by clinicians [1].

SUMMARY

Aminazine (Chlorpromazine) in doses of 1 mg per kilogram of body weight decreases the death of white mice from traumatic shock by 45%, mepazine by 20%, morphine by 42%. Higher doses of these preparations do not increase the percentage of survival of these animals.

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