PHARMACOLOGY

THE EFFECT OF SOME PHENOTHIAZINE DERVATIVES ON THE DEVELOPMENT OF EXPERIMENTAL TOXIC EDEMA OF THE LUNGS

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There have recently appeared clinical and experimental studies in which attention is drawn to the successful use of derivatives of phenothiazine for therapy of pulmonary edema of various origins.

A. Decortis [5] observed two clinical cases where they treated severe edema of the lungs by the introduction of a lytic mixture proposed by H. Labori and P. Huguenard (chlorpromazine, promethazine, diethazine). There are also similar communications concerning the effectiveness of chlorpromazine, pacatal* [6], and promethazine in the treatment of experimental edema of the lungs.

In the present study we presented ourselves with the problem of comparing the effectiveness of aminazine,* mepazine, its chlorinated derivative, and promethazine in experimental therapy of toxic edema of the lungs.

METHODS AND RESULTS

Mepazine (synonym, pacatal) and its chlorinated derivative were synthesized in the Institute of Pharmacology and Chemotherapy of the USSR Academy of Medical Sciences. We studied the action of each preparation in experimental edema of the lungs produced by adrenalin in white mice, and pulmonary edema resulting from the administration of ammonium chloride to white rats.

In different series the number of animals was different, but sufficient for statistical reliability of the results.

Pulmonary edema produced by adrenalin. The first series of experiments (20 mice) served as a control. We produced adrenalin edema of the lungs by the administration of the official preparation of adrenalin in 0.1% solution in the amount of 10 mg/kg of body weight. About half of the animals of this series succumbed in 8-59 minutes; we killed the others by decapitation an hour after administration of the adrenalin. In all cases we examined the lungs carefully, removed them and weighed them. In addition to the macroscopic picture of edema of the lungs (swelling, blotchiness, hemorrhage, and flow of foamy liquid from incised organ), we determined the weight of the lungs as a percentage of body weight (K). Normally this amounts to 0.7-0.9. In the experiments of the control series it was higher than 1.25, in some cases going as high as 2.03-2.31. The average value of K for the control series was 1.59.

In the second series of experiments (20 mice), about an hour before intraperitoneal injection of the adrenalin we administered aminazine in the amount of 10 mg/kg body weight. At the time the adrenalin was injected the mice were sluggish, immobile, and in a state suggesting drowiness. In 16 cases edema did not develop, in 3 cases the symptoms of edema were slight, in 1 case marked. Average value of K., 0.83.

* Russian trade name.

In the third series of experiments we administered a subcutaneous injection of adrenalin about an hour after administration of mepazine. In a dose of 50 mg/kg (20 mice), in 8 cases mepazine completely prevented the development of edema, in 12 cases there was edema with K = 1.14 (average value) in a dose of 100 mg/kg (12 mice), in 9 cases mepazine prevented the development of edema; in 3 cases edema was observed. Average value of K, 0.99. The preparation, administered in the same dose intraperitoneally (9 mice) in all cases prevented the development of edema; K was 0.75 (average value).

In the fourth series of experiments we studied the action of the chlorinated derivative of mepazine (100 mg/kg). When injected subcutaneously (10 mice), this preparation in 1 case prevented the development of edema, in 4 cases the edema was mild, in 5 marked; average value of K = 1.28. Intraperitoneal administration (8 mice) of the preparation completely prevented the development of edema; K = 0.79 (average value).

In the fifth series of experiments (9 mice) we employed the subcutaneous injection of 50 mg per kg of promethazine to prevent edema. In 3 cases edema did not develop, in two it was mild, in 4 cases, marked; K = 1.24 (average value).

Pulmonary edema produced by ammonium chloride. We injected ammonium chloride intraperitoneally in the amount of 0.70-0.75 ml of a 6% solution per 100 g body weight. In the first (control) series of experiments (31 rats), in the majority of cases (one exception) the symptoms of edema were strongly pronounced. The magnitude of K ranged from 0.68 to 2.21 with an average value of 1.47.

In the second series of experiments, about an hour before the administration of the ammonium chloride we injected 10-20 mg/kg of aminazine subcutaneously. In a dose of 10 mg/kg (20 rats) aminazine in 15 cases completely prevented the development of edema, in 3 cases edema was slight, and in only two pronounced; the average value of K was 0.89. Administration of 20 mg/kg of aminazine (10 rats) averted toxic edema in 9 cases; average value of K = 0.74.

In the third series of experiments we studied the action of 50 and 100 mg/kg of mepazine when injected subcutaneously. Following the injection of 50 mg/kg (11 rats), edema did not develop in 4 cases, was mild in 5 cases; K = 1.04 (average value). Following the injection of 100 mg/kg (14 rats), there was no edema in 10 cases; K = 0.96.

In the fourth series of experiments the subcutaneous injection of 50 mg/kg of the chlorinated derivative of mepazine (13 rats) prevented the development of edema in 10 cases; K = 0.85 (average value).

In the fifth series of experiments we administered 50 mg/kg of promethazine (10 rats). In 7 cases edema did not develop, in 1 case it was mild, and in two moderate; K = 1.06 (average value).

In addition to the magnitude of K, the survival of the animals may serve as an index of the effectiveness of the preparations. In the control experiments about half of the animals succumbed in the hour after the administration of the edema-provoking substance. In all cases where we used derivatives of phenothiazine death of the animal was not observed.

Thus all the derivatives of phenothiazine investigated by us possess the ability to delay the development of pulmonary edema. The strongest inhibiting action, from both points of view, of experimental edema is displayed by the intraperitoneal or subcutaneous injection of aminazine in doses of 10 and 20 mg/kg. Subcutaneous injection of 50 and 100 mg/kg of mepazine also inhibits the development of pulmonary edema. The chlorinated derivative of mepazine (100 mg/kg subcutaneously) acts more weakly on adrenalin edema, but no less effectively on edema produced by ammonium chloride.

The experiments with promethazine gave in both cases very contradictory results; in this case statistical reliability is lacking. We therefore limit our discussion to the weaker action of promethazine as compared with the other preparations.

In the literature [1, 2, 3, 4] there are found statements that many narcotic substances can prevent the development of toxic pulmonary edema, but for this a considerable depth of narcosis is necessary. Judging by our data, a state of narcosis is not necessary for the production of the antiedema effect. Derivatives of phenothiazine not possessing narcotic action also appear to be effective in the experimental therapy of acute toxic edema of the lungs.

SUMMARY

Preparations of the phenothiazine group, aminazine, mepazine, a chlorinated derivative of mepazine, and promethazine inhibit the development of experimental toxic edema of the lungs, producted by adrenalin and by NH_4Cl. Aminazine is the most effective preparation, promethazine the least effective.

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* Original Russian pagination. See C. B. translation.