# EFFECT OF THE MONOAMINE OXIDASE INHIBITOR INDOPAN ON EXPERIMENTAL PNEUMOCOCCAL INFECTION IN RATS

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The study of the effect of monoamine oxidase inhibitors on the course and outcome of bacterial infection is of great practical and theoretical importance. First, these inhibitors are used in the clinical management of cardiovascular, neurological, psychiatric, rheumatoid, and other diseases, in which the agent of the infection may play the role of an etiological factor or may give rise to complication. Second, they raise the concentration of serotonin and catecholamines in the organism, and some of them raise the histamine level, all substances playing an important part in the pathogenesis of the infectious process [3,4,5,10-13]. The authors have shown that iproniazid, a long-acting monoamine oxidase inhibitor, increases the sensitivity of animals to pneumococcal infection and to the action of typhoid toxin [6].

The object of the present investigation was to study the effect of indopan [2,8], a monoamine oxidase inhibitor which is more effective than iproniazid but with a shorter action, on the course and outcome of a bacterial infection, and to determine whether this effect is dependent on its property of inhibiting monoamine oxidase activity.

## EXPERIMENTAL METHOD

The work was carried out on 330 albino rats weighing 180-200 g. The animals were divided into the following 11 equal groups: 1st, infected with pneumococcus, 2nd, receiving indopan, 3rd, infected with pneumococcus and receiving indopan, 4th, infected with pneumococcus and receiving mexamine, 5th, infected with pneumococcus and receiving indopan and mexamine, 6th, receiving mexamine, 7th, receiving indopan and mexamine, 8th, infected with pneumococcus*, 9th, infected with pneumococcus and receiving cyproheptadine, 10th, infected with pneumococcus and receiving indopan and cyproheptadine, 11th, receiving cyproheptadine.

An injection of pneumococcus type 1 was given subcutaneously into the animals' right side in a dose of 0.1 ml of an 18-h culture, diluted 1:100; indopan was injected subcutaneously in a dose of 33.3 mg/kg, 2 h before infection and 6, 24, and 30 h after infection with pneumococcus; mexamine was given subcutaneously in a dose of 50 mg/kg four times daily at intervals of 2 h during the day; cyproheptadine was given intramuscularly in a dose of 150 mg/kg three times daily at intervals of 3 h for 4 days. The first injection of mexamine and cyproheptadine was given 1 h after the injection of indopan, i.e., 1 h before infection with pneumococcus. The control groups of rats received injections of the preparations in the same doses and in the same order as the experimental groups. The indopan and mexamine used in the experiments were prepared at the Ordzhonikidze All-Union Research Chemo-Pharmaceutic Institute and the cyproheptadine hydrochloride was manufactured by the firm of Merck (United States).

The action of the preparations was judged from the animals' general condition and the time of their death. Observations were continued for 15 days. The results obtained were given in the form of curves; the significance of the results was verified by statistical analysis using the method of calculation of the $\chi^2$ criterion ($P < 0.05$; $P = 0.01$).

*Experiments with cyproheptadine and indopan were carried out on this group of animals; the results of the experiments did not coincide in time with those carried out with indopan and mexamine.

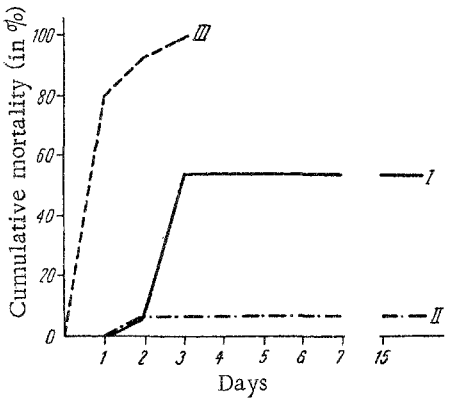


Fig. 1. Effect of indopan on mortality among rats with pneumococcal infection: I) animals infected with pneumococcus; II) receiving indopan; III) infected with pneumococcus and receiving indopan.

Two hours after the first injection, indopan caused general excitation, intensive motor activity, and untidiness of the hair in the rats (control and experimental). Six hours after the first injection, the animals showed intensive depression, apathy, lowering of the body temperature, and abundant moisture on the body (the skin was wet). These phenomena persisted during the subsequent injections of indopan next day. Indopan greatly increased the sensitivity of the rats to experimental pneumococcal infection, accelerating death and increasing the proportions of animals which died (Fig. 1). The rats receiving indopan died 8-12 h after infection with pneumococcus. In the third group, 24 h after infection with pneumococcus, 80% of the animals died, whereas in the 1st and 8th group, all the rats survived. Two days after infection with pneumococcus, 93.3% of the rats in the 3rd group had died and 6.6% of the rats in the 1st and 2nd group. At the end of the 3rd day after infection with pneumococcus, all the animals in the 3rd group had died, but only 53.3% in the 1st, and 6.6% of the animals in the 2nd group. The survival rate among the rats was 46.7% in the first group and 93.3% in the 2nd group.

Since the stimulant action of indopan on the central nervous system does not coincide with its phase of monoamine oxidase inhibition, it was interesting to determine with which property of indopan the increase in the sensitivity of the rats to infection was associated, with its action as a monoamine oxidase inhibitor or with its anti-depressive action on the central nervous system. For this purpose, experiments were carried out with mexamine [7], which in some respects is an antagonist of indopan in its action on the central nervous system [1], while otherwise it is similar in its effect to serotonin although weaker in its action, and similar to cyproheptadine, an antagonist of serotonin and histamine [9,14].

Mexamine (Fig. 2), in the dosage used, had no toxic action on healthy animals but significantly increased the sensitivity of the rats to pneumococcal infection. For instance, on the second day of the disease 40% of the animals in the third group had died and 86.6% in the 4th group, whereas the mortality rates in the 2nd and 1st groups were 6.6 and 53.3% of rats, respectively.

Indopan and mexamine, when given together, proved toxic to the healthy rats; 93.3% of the animals of the 7th group died in the first day. In the 5th group, 40% of the rats died before injection of the bacteria, i.e., during the first h after injection of indopan and mexamine, and 53.3% died within a few h after infection with pneumococcus.

The experiments to study the combined action of cyproheptadine and indopan (Fig. 3) showed that cyproheptadine, in the dosage used, did not prevent the negative action of indopan on the rats infected with pneumococcus. After pneumococcal infection, the curve of mortality among the rats receiving indopan and cyproheptadine was close to the curve of mortality of the rats receiving indopan alone. The mortality among the animals in the 10th group reached 100% only on the 6th day, compared with the 3rd day after infection of the rats with pneumococcus in the 3rd group. At the same time, cyproheptadine, itself, lowered the mortality among the rats from pneumococcal infection.

It may be concluded from the results obtained that one of the causes of the increased sensitivity of animals to infection as a result of the action of indopan is its property of depressing monoamine oxidase activity and thereby of raising the level of serotonin and of other biogenic amines in the body.

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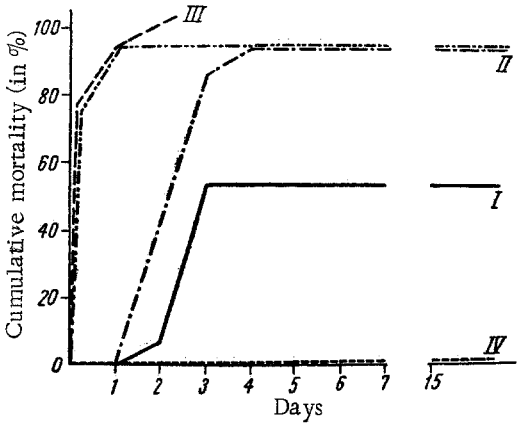


Fig. 2. Effect of indopan and mexamine on mortality among rats with pneumococcal infection: I) animals infected with pneumococcus; II) infected with pneumoccus and receiving mexamine; III) infected with pneumococcus and receiving indopan and mexamine; IV) receiving mexamine; V) receiving indopan and mexamine.

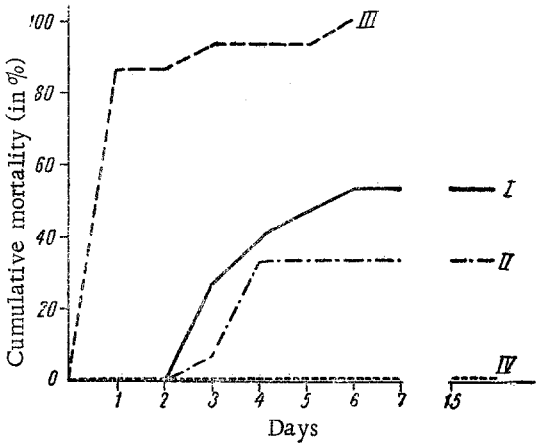


Fig. 3. Effect of indopan and cyproheptadine on mortality among rats with pneumococcal infection: I) animals infected pneumococcus; II) infected with pneumococcus and receiving cyproheptadine; III) infected with pneumococcus and receiving indopan and cyproheptadine; IV) not infected with pneumococcus and receiving cyproheptadine.


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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

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