EXPERIMENTAL INVESTIGATION OF THE ANTITUBERCULOUS ACTIVITY OF CHLORPROMAZINE

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During the treatment of patients suffering simultaneously from schizophrenia and pulmonary tuberculosis with chlorpromazine, the drug was found to have a favorable effect on the course of the tuberculosis [10]. In vitro, chlorpromazine inhibited the propagation of Mycobacterium tuberculosis. Reports have recently been published [1, 3, 5, 6, 8, 9, 11, 12] indicating that the combined treatment of patients with pulmonary tuberculosis with chlorpromazine and antibacterial preparations led to the more rapid resolution of the inflammatory changes and to closure of the cavities. In a dose of 20 mg/kg, chlorpromazine was found to prevent the breakdown of tuberculous infiltration in sensitized dogs [2].

The object of the present investigation was to study the character of the effect of chlorpromazine on the course of tuberculosis.

EXPERIMENTAL METHOD AND RESULTS

The study of the bacteriostatic activity of chlorpromazine. The action of chlorpromazine on growth of M. tuberculosis (strains bovinus-8 and $H_{37}Rv$) in Sutton's liquid nutrient medium was investigated in concentrations 1, 5, 10, 50, 100, 500, 1000, and 5000 μg/ml. To each tube 0.1 mg of the culture was added Total suppression of growth of strain bovinus-8 was observed by chlorpromazine in concentrations of 5 μg/ml nutrient medium or more. Growth of strain $H_{37}Rv$ was depressed by a concentration of 5 μg/ml and totally suppressed by concentrations of 10 μg/ml or more.

Investigation of the effect of chlorpromazine on the course of tuberculosis in albino mice. In these experiments 90 albino mice with a mean weight of 20-22 g were inoculated intravenously with 0.1 mg of a 3-week culture of strain bovinus-8.

The animals as a whole were subdivided into 6 groups (15 animals in each group). The mice of group 1 (control) were untreated. The animals of group 2 received 0.05 mg chlorpromazine each, the mice of group 3 received 0.05 mg chlorpromazine and 1000 units streptomycin. The animals of group 4 received 0.25 mg chlorpromazine each, the animals of group 5 received 0.25 mg chlorpromazine and 1000 units streptomycin each, and the mice of group 6 received only streptomycin.

The treatment began 48 h after inoculation and was given daily except Sundays for 2.5 months, after which all the surviving mice were sacrificed. Chlorpromazine was injected intramuscularly and streptomycin subcutaneously. The minimal dose of chlorpromazine (0.05 mg), when saturated in relation to body weight corresponded approximately to the recommended clinical therapeutic dose. The maximal dose was 5 times greater and was toxic: it caused drowsiness and shivering in the animals and led to the development of inflammatory infiltration at the site of injection. The dose of streptomycin chosen was less than the therapeutic dose [4].

The results of investigation of the dying or sacrificed animals showed that chlorpromazine had no effect on the life span or weight of the animals, on the weight of their lungs, the index of morbidity of the lungs, or the number of tubercle bacilli found in them. The therapeutic effect of a combination of chlorpromazine and streptomycin was equal to the effect of streptomycin alone. Histological investigations showed that chlorpromazine had no significant effect on the course of tuberculosis in mice. Admittedly, among the mice receiving 0.25 mg chlorpromazine, a mainly productive form of the disease was observed rather more frequently (in 67% compared with 47% of cases in the control series) but the difference was not significant ($P > 0.2$).

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Investigation of the effect of intramuscular injection of chlorpromazine on tuberculin sensitivity of the skin. This effect of chlorpromazine was studied in guinea pigs (43) inoculated subcutaneously with strain $H_{37}Rv$ in a dose of 0.005 mg; 14 of these animals were left as controls (group 1). Group 2 (14 guinea pigs) received chlorpromazine starting on the day after inoculation. The animals of group 3 received chlorpromazine from the moment of appearance of a positive reaction to tuberculin. In addition, 6 guinea pigs were inoculated with strain bovinus-8 in a dose of 0.000001 mg; they began to receive chlorpromazine 4 months after inoculation. All the animals received the preparation by intramuscular injection in a dose of 5 mg once daily except on Sundays. The intradermal tests began with liquid tuberculin prepared in synthetic medium in a dilution of 1 :10; the size of the area of infiltration was measured 48 h later.

Chlorpromazine did not delay the appearance of tuberculin allergy in the animals of group 2. However, in the period of administration of chlorpromazine to the animals a marked diminution of the reaction to tuberculin and disappearance of the necrotic component were observed. One month after inoculation (and the beginning of treatment) the mean diameter of the papules was 12 mm compared with 16 mm in the control. The difference was significant ($P < 0.05$).

Before administration of chlorpromazine the mean diameter of the tuberculin papules in the guinea pigs of group 3 was 19 mm, and necrosis was seen in the center of the papules in 10 animals. After treatment for 3 weeks the diameter of the papules in the animals of group,3 and 8 mm ($P > 0.001$), and after 1 month – 8 mm ($P > 0.001$). No necrotic reaction was seen at these times.

In the guinea pigs inoculated with a minimal dose of M. tuberculosis, the maximal diameter of the papules before treatment began was 14 mm, falling to 10 mm after 2 weeks. After treatment for 5 weeks, in 5 of the 6 guinea pigs complete suppression of tuberculin sensitivity was observed, and in 1 animal the diameter of the papule was smaller ($P > 0.001$). After the chlorpromazine had been discontinued, the animals gradually recovered their sensitivity to tuberculin.

Investigations of the effect of local administration of chlorpromazine on the skin reaction to tuberculin. Infected guinea pigs [13] were injected intradermally with 0.1 ml tuberculin in a dilution of 1 :10. On one side of the trunk tuberculin only was injected, and on the opposite side (in 7 animals on the left, in 6 on the right) tuberculin diluted with 2.5% chlorpromazine solution. Local administration of chlorpromazine was found to diminish the intensity of tuberculin reaction. The mean maximal diameter of the papules following injection of tuberculin was 14 mm, and after injection of tuberculin with chlorpromazine it was 9 mm. The difference is significant ($P > 0.001$).

The results of the histological investigation of biopsy specimens of the papules from 13 animals (of which 3 received chlorpromazine intradermally and 5 intramuscularly, while 5 guinea pigs were controls) showed that all the animals developed dermatitis at the site of injection of the tuberculin. In the animals receiving chlorpromazine, the inflammatory changes were less severe, and no ulceration or oozing of pus or fibrin was observed, as was found in the control animals. In the doses used, close to those adopted clinically, chlorpromazine thus had no marked effect on the course of tuberculosis in the animals. The results of the experiments on mice were in general agreement with those obtained by other authors [7, 13, 14]. Admittedly, an inhibitory action of chlorpromazine on the course of tuberculosis in guinea pigs had been reported [14], but only when very high, toxic doses of the preparation (up to 40 mg/kg) were used. The toxicity of this preparation prevents its use in doses necessary for establishing a bacteriostatic concentration in the blood stream of patients with tuberculosis.

The beneficial effect observed clinically in patients with tuberculosis following administration of chlorpromazine is probably due to the effect of this preparation on the complex mechanism of neurohumoral regulation, which plays a far more important role in the pathogenesis of tuberculosis in man than in animals.

Changes in the allergic reactivity of the body largely determine the pattern of tuberculous infection in man (the clear subdivision into primary and secondary stages, the formation of zones of local hypersensitization, cavity formation, and so on). The depression of tuberculin sensitivity by chlorpromazine revealed by these investigations suggests that this drug should be given to patients to whom tuberculosis is accompanied by marked hyperergia.

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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 the first issue of this year.
