IMMUNOCORRECTIVE PROPERTIES OF ANTIBIOTICS IN SECONDARY IMMUNODEFICIENCY

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The unanimity of interpretations of the immunotropic activity of antibiotics is no longer in dispute. In the classical view, antibiotics are immunodepressants. However, analysis of the literature shows a few publications which directly or indirectly question this proposition. The writers previously describe experimental proof of the presence of immunostimulating properties among the β-lactam and aminoglycoside antibiotics, which are the most widely used groups of these substances. However, the question of the immunocorrective activity of antibiotics remains open. There have been only a few publications indicating that antibiotics may probably possess this property [2, 8]. Research in this field has been carried out with the use of only therapeutic (bactericidal) doses of antibiotics, administered frequently. It seemed worth while to study the immunocorrective properties of antibiotics given in different doses and by different methods. This paper describes the results of a study of the effect of a wide range of doses of the two main groups of antibiotics: β-lactam (penicillin) and aminoglycoside (streptomycin, gentamicin) [3, 4], given in a single dose, on the immune response in mice with cyclophosphamide-induced immunodeficiency.

EXPERIMENTAL METHOD

Experiments were carried out on first-generation hybrid (CBA × C57BL/6J)F_1 mice free from any specific bacterial carrier state. The following antibiotics were used: benzylpencillin, sodium salt; streptomycin sulfate, and gentamicin sulfate. The antibiotics were injected intraperitoneally in 0.9% isotonic sodium chloride solution in a single dose ranging from 0.5 to 500,000 U/kg. The study was undertaken on an experimental model of secondary immunodeficiency, leading to lowering of all parameters of cellular and humoral immunity [1]. For this purpose the mice were given injections of the cytostatic agent cyclophosphamide (CP) intraperitoneally in a dose of 0.05 g/kg daily for 3 days. The antibiotics were injected after the last injection of the cytostatic. Changes in parameters of the humoral immune response were assessed on the basis of production of antibody-forming cells (AFC), by the method of direct local hemolysis [7]. The antibiotics were injected into the mice simultaneously with 0.02% sheep's red blood cells (SRBC). Changes in the parameters of the cell-mediated immune response were assessed on the basis of the change in intensity of the delayed-type hypersensitivity reaction (DTHR) [5]. The mice were immunized intraperitoneally with 0.2% SRBC. The antibiotics were injected simultaneously. The reacting injection consisted of 1.0% SRBC. Phagocytic activity of peritoneal macrophages (PMP) was assessed morphologically by light microscopy [6]. This type of activity was assessed from the intensity of phagocytosis of heat-killed cultures of *Staphylococcus aureus,* with determination of Hamburger's index (HI) – the number of actively phagocytic PMP as a percentage of their total number. The results were subjected to statistical analysis by the Student Fisher test.

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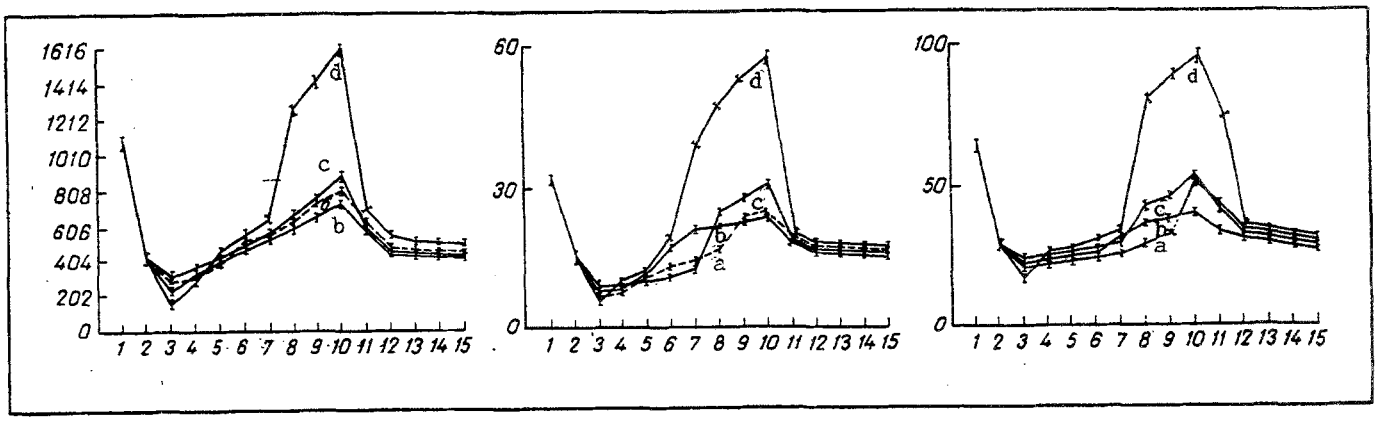

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Effect of antibiotics on AFC formation in spleens of mice with CP-induced immunodeficiency. Abscissa, doses of antibiotics (U/kg): 1) control (intact), 2) control (CP), dose (in U): 3) 500,000, 4) 250,000, 5) 50,000, 6) 25,000, 7) 5000, 8) 2500, 9) 500, 10) 250, 11) 50, 12) 25, 13) 5, 14) 2.5, 15) 0.5; a) penicillin, b) gentarnicin, c) streptomycin, d) penicillin + streptomycin; ordinate, number of AFC per spleen.

Fig. 2. Effect of antibiotics on DTHR formation in mice with CP-induced immunodeficiency. Abscissa, doses of antibiotics (U/kg): 1) control (intact), 2) control (CP), 3) 500,000, 4) 250,000, 5) 50,000, 6) 25,000, 7) 5000, 8) 2500, 9) 500, 10) 250, 11) 50, 12) 25, 13) 5, 14) 2.5, 15) 0.5; a) gentamicin, b) streptomycin, c) penicillin, d) penicillin + streptomycin: ordinate. index of reaction (per cent).

Fig. 3. Effect of antibiotics on phagocytic activity of PMP in CP-induced immunodeficiency. Abscissa, doses of antibiotics (U/kg): 1) control (intact), 2) control (CP), 3) 500,000, 4) 250,000, 5) 50,000, 6) 25,000, 7) 5000, 8) 2500, 9) 500, 10) 250, 11) 50, 12) 25, 13) 5, 14) 2.5, 15) 0.5; a) gentamicin, b) streptomycin, c) penicillin, d) pencillin + sptreptomycin; ordinate: Hamburger's index (per cent).

EXPERIMENTAL RESULTS

As Fig. 2 shows, CP inhibited AFC formation in the spleen of the mice by 2.6 ($p < 0.001$) times. The use of antibiotics against this background led to either strengthening or weakening of this action or to its total abolition, and the effect was dose-dependent in character. For instance, the antibiotics intensified the inhibitory action of CP on AEC formation in the maximal bactericidal dose: 500,000 U/kg, by 1.43 ($p < 0.05$) to 1.9 ($p < 0.001$) times. The combined use of penicillin and streptomycin potentiated this action by 2.8 ($p < 0.001$) times. In subbactericidal doses the antibiotics exhibited marked immunocorrective activity. They increased AFC production by 1.38 ($p < 0.05$) — 2.1 ($p < 0.001$) times compared with the CP-treated control. When penicillin and streptomycin were given together, their action was synergic. For instance, subbacterial doses of 2500-50 U/kg stimulated AFC production by between 1.6 ($p < 0.05$) and 3.8 ($p < 0.001$) times. The remaining doses of antibiotics caused no significant change in levels of AFC production ($p > 0.05$).

As Fig. 2 shows, CP inhibited DTHR formation by 2.1 ($p < 0.001$) times. The use of antibiotics against this background led to changes in the reaction index (RI) which was dose-dependent. For instance, maximal bactericidal doses of 500,000 U/kg and 250,000 U/kg (gentamicin only) potentiated the inhibitory action of CP by between 1.9 ($p < 0.05$) and 2.2 ($p < 0.05$) times. In response to the combined administration of penicillin and streptomycin in a dose of 500,000 U/kg, this parameter fell by 2.54 ($p < 0.001$) times. Subbactericidal doses of the antibiotics (2500-250 U/kg) exhibited marked immunocorrective properties. They increased RI compared with the CP-treated control by between 1.4 ($p < 0.05$) and 1.96 ($p < 0.001$) times. In response to combined administration of penicillin and streptomycin, a synergic action was demonstrated: RI was increased by 3.1-3.7 ($p < 0.001$) times. The remaining doses of the antibiotics had no significant effect on DTHR formation ($p > 0.05$).

It will be clear from Fig. 3 that CP inhibited HI by 2.2 ($p < 0.001$) times. Maximal bactericidal doses of the antibiotics, namely 500,000 and 250,000 U/kg, inhibited HI by between 1.16 ($p < 0.05$) and 1.28 ($p < 0.001$) times. Combined administration of penicillin and streptomycin lowered HI by 1.8 ($p < 0.001$) and 1.16 ($p < 0.05$) times. In subbactericidal doses, namely 250,000-25 U/kg, the antibiotics exhibited marked immunocorrective properties. They increased HI compared with the CP-treated control by between 1.16 ($p < 0.05$) and 1.87 ($p < 0.001$) times. Combined use of penicillin and streptomycin led to the manifestation of a synergic effect: HI was increased by between 1.17 ($p < 0.05$) and 3.3 ($p < 0.001$) times. The remaining doses of the antibiotics did not change HI significantly ($p > 0.05$).

The investigation thus showed that antibiotics possess marked immunocorrective properties. These properties of antibiotics are exhibited when they are given in subbacterial/subtherapeutic doses, in both humoral and cell-mediated immune response. The synergic action of penicillin and streptomycin when given in combination, and which is exhibited only in subbacericidal doses, is in our view noteworthy. Analysis of immunopharmacologic parameters of the immunocorrective action of antibiotics suggests that streptomycin and gentamicin affect mainly the humoral component, and penicillin the cellular component of the immune response.

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