Kekkaku Vol. 52, No. 7

ANTITUBERCULOUS EFFECT OF HISTIDINE

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(Received for publication January 22, 1977)

It was shown by Abdel Kader and Zaki[1)~5)] that histidine (*in vitro*), tryptophan and some of its metabolites (both *in vitro* and *in vivo*) possessed bacteriostatic effect on mycobacterium tuberculosis. Histidine is now gaining a site in researches done on human tuberculosis. Kulyabko[9)] found increased histamine level in blood in acute primary tuberculosis in young children. This investigation was, therefore, conducted to study the effect of histidine on tuberculosis in guinea pigs.

EXPERIMENTAL

The experiment was done on guinea pigs that were selected from the laboratory stock. 32 guinea pigs of the male sex weighing from 250 to 300 g were selected and kept on a stock diet composed of rye and green clover during the experimental period. The animals were housed separately, each group per cage. All animals were infected with 0.001 mg of virulent strain of Mycobacterium tuberculosis bovis by intramuscular injection in the right thigh. The animals were divided into four groups, 8 animals each. The first group (I) was used as a control infected group, the second group (II) was simultaneously treated with intramuscular injection of streptomycin three times a week and 5 mg isonicotinyl hydrazide (INH) orally daily. Treatment was performed immediately after infection.

The third group (III) was given a daily subcutaneous dose of 50 mg L-histidine, as 1 m*l* sterile aquous solution for a period of 15 days immediately after infection.

The fourth group (IV) was given the same dose of histidine 15 days after infection for a period of 15 days. The experimental period was 8 weeks, and the animals were then sacrificed and examined. The technique of Feldman and Hinshaw[7)] was exactly followed for all groups of animals studied. All guinea pigs were examined at autopsy and, in all, sections of lymph nodes, spleen and liver were stained and microscopically examined.

RESULTS

On post-mortem examination the control infected animals (group I) showed evidences of infection manifested by enlargement and caseation with generalization specially in spleen and liver. Films were made and stained with Ziehl-Nelsen and examined microscopically and revealed the presence of T. B. organisms. The lungs, as well, showed discrete tubercles, discrete alveolar obstruction and increased vascularity.

The animals of group II (streptomycin and INH) did not show signs of generalization, and the regional lymph nodes were slightly enlarged, fibrosed and showed no caseation. Microscopic examination revealed normal spleen and liver, but the lungs showed multiple tubercles and consolidation of 2/3 of lung tissue (+++). There was also increased vascularity in the lung tissue. The histidine-treated group(III), however, showed a normal spleen; the liver showed no caseation, but small areas of central atrophy (+) were present. The lung tissue in this group was normal with occasional areas of increased vascularity.

Group IV treated with histidine 15 days after infection showed normal spleen, areas of hepatic central atrophy (++) and the lungs showed few scattered tubercles limited by thick fibrous tissue and immature new alveoli.

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Table 1. Degree of Pathological Lesion in Different Organs of Different Groups of Guinea Pigs

Group examined	Lymph nodes	Spleen	Liver	Lung	Total degree of activity
Control	++++	++++	++++	++	(++++)
Streptomycin+INH treated group	1/2−+	−	−	+++	(++)
Immediately histidine treated group	1/2−+	−	+	−	No activity, but minor liver atrophy (−)
Histidine group treated 15 days after infection	+	−	++	+	(+) moderate Moderate liver atrophy (+)

DISCUSSION

The infected, non-treated, control group showed a picture similar to that described by many authors[8].

The microscopic picture of the organs of group II animals (streptomycin +INH treated animals), showed normal spleen and liver, but there was exacerbation in the tuberculous reaction of the lung tissue manifested by the presence of multiple tubercles and consolidation of 2/3 of lung tissue(+++). This exacerbation in the pulmonary tuberculous picture, found 6 weeks after stopping the treatment and which was not found in the nontreated tuberculous animals (group I), denoted diminished tissue resistance. This exacerbation might be similar to the remission which occurs in human tuberculosis, whenever the antituberculous treatment is not continued for at least one year[10]. In this group of animals, the traditional anti-tuberculous drugs were able to erode the disease from both spleen and liver without any remission after stopping them. But this was not the case with the lung, which did not gain prolonged immunity and the flaring of the pulmonary condition probably happened during the one and half months following the short therapeutic period.

That the histidine immediately treated animals (group III) showed no manifestations of active tuberculosis in any organ, denoted increased tissue resistance that prevented any recurrence of tuberculous picture after the short period of treatment (15 days).

Group IV animals which were treated with histidine 15 days after infection, showed fibrous tissue formation around the few scattered tubercles in the lung. Fibrosis is a sign of limitation of infection and increased resistance[6]. There was as well new alveolar formation denoting a trial for generation.

The presence of central liver atrophy of varying degree is a considerable disadvantage, although it is not a sign of tuberculous activity. That histidine did not completely save the liver cells (atrophy +) to the same extent as streptomycin INH (normal), might be attributed to one of either causes. It might just be an end to the acute massive necrosis caused by the tubercle bacillus as in experimental acute necrosis[11)~13)] of liver, which being antagonized by the massive doses of histidine could not be completely cured due to the extrametabolic burden of the big dose of histidine on the massively caseated liver tissue. Fortunately the atrophy is not as massive as the necrosis and liver affection is not a feature in the pathogenicity of the tubercle bacillus in other mammals including Man.

These findings would have proved that the therapeutic effect of histidine is better than that of streptomycin INH if we could prevent the central hepatic atrophy. For this purpose, experimental trials are being undertaken.

The mechanism of histidine action in combating tuberculosis may probably involve two mechanisms; namely bacteriostatic effect[1] and secondly by raising local immunity of tissues as evident by absence of flaring of pulmonary condition. On the contrary there are signs of resistance and repair.

Work is in progress to study further effects of histidine and of its metabolites on tuberculosis.

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