Kekkaku Vol. 54, No. 8

ANTITUBERCULOUS EFFECT OF HISTAMINE

M.M. Abdel KADER*, Kawther M.S., S. SHOUB, B.A. El-MOURSI and F. HALAWA

(Received for publication April 2, 1979)

Histidine was shown to have a potent anti-tuberculous action in vitro[1] and in vivo[9]. The antituberculous effect of some histidine derivatives were further tested, in vitro[10]. Of these derivatives, imidazole and histamine presented high potency in their antituberculous action in vitro. The in vivo effect of imidazole[10] was subsequently investigated.

This investigation was further conducted to study the in vivo action of histamine in guinea-pigs, in order to compare it with those previously shown by histidine and imidazole.

Experimental Method

The experiment was done on guinea pigs 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 0.001mg 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 an untreated control 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 0.15 mg of histamine, as 1m*l* sterile aqueous solution for a period of 15 days immediately after infection.

The fourth group (IV) was given the same dose of histamine 15 days after infection for a period of 15 days. The experimental period was 8 weeks, and the animals were sacrificed and examined.

The technique of Feldman and Hinshaw[13] was exactly followed for all groups of animals studied. All guinea pigs were examined at autopsy and all sections of lymphnodes and liver were stained and microscopically examined.

Results

The results are summarized in Table 1. On post-mortem examination of the control animals (group I), evidence of infection was manifested by enlargement and caseation with generalization specially of spleen and liver. Films made and stained with Ziehl-Neelsen and examined microscopically 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 & INH) did not show signs of generalization, and the regional lymphnodes 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 histamine treated group (III) showed, normal liver, spleen and lung except congestion in the three organs. Even the lung showed only increased vascularity not mounting to congestion. Group (IV) treated with histanine 15 days after infection, however, showed microscopic signs of tuberculosis. The lungs presented follicles of chronic inflammatory cells with no giant cells (++) accompanied by congestion of the pulmonary tissue. The liver presented patchy subcapsular necrosis (+) and congestion of the central vein. The spleen as well showed areas of necrosis.

* From the Biochemistry and Bacteriology Departments, Faculty of Medicine & Cancer Institute, Cairo University, Cairo, Egypt.

Table 1. Degree of Pathological Lesions in Different Organs of Different Groups of Guinea-pigs

Group examined	Lymph nodes	Spleen	Liver	Lung	Total degree of activity
I. Control	++++	++++	++++	++	(++++)
II. Streptomycin + INH treated group.	1/2 −+	−	−	+++	(++)
III. Histamine group starting treatment immediately after infection.	−	−	−	−	No activity, only congestion
IV. Histamine group starting treatment 15 days after infection.	1/2 ±	+	+	++	Activity (++)

Discussion

The infected untreated control group showed a picture similar to that described by many authors.

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 reactions 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 untreated 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. 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.

The fact that the histamine 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 in which treatment with histamine was started 15 days after infection, showed microscopic manifestation of tuberculous necrosis in the liver and spleen (+) while the lesions of the lung was (++). Comparing the results of both groups treated with histamine (III & IV), one can say that histamine was highly potent in the treatment of acute stages of experimental tuberculosis while its potency lagged behind when the administration was started 15 days after infection.

Previous work on histamine and imidazole[10] proved that imidazole was, in fact, the most potent tuberculostatic agent compared to other derivatives. It also proved that the presence of an animated side chain did not affect its tuberculostatic potency, while those having non-aminated side chains showed low potency[10]. The previous in vivo studies showed the untoward toxic hepatic effect of histidine[9] and imidazole[10].

It is clear that the decarboxylation of histidine raised the biological activity of the resulting histamine as a tuberculostatic agent. It fact, histanine proved to be six times as effective as imidazole and more than 100 times as histidine. The use of very small therapeutic doses of histamine saved its otherwise drastic side effect (LD 50 2.5mg/guinea pig)[14].

The present work proved that histamine is more effective as a tuberculostatic agent when given immediately than histidine, since it did not show any sign of hepatic fibrosis which was previously noted by histidine[9].

Besides the antituberculous effect of small doses of histamine, Kahlson[15] and Rosengreen showed that histamine was probably involved in tissue repair.

All experimental edivence proved the high potency of histamine as a tuberculostatic agent in comparatively small therapeutic doses. Kalybko[16] showed that the concentration of histamine in the blood of children with acute tuberculosis was significantly increased. The increased concentration of blood histamine, together with its proved tuberculostatic effect might be one of the endogenous defense biochemical mechanisms against the invading mycobacterium.

The same applies to the tuberculostatic effect of indole and its derivatives[1)~5)6)]. The sputum and urine of

tuberculous patients contain high amounts of indole[22]. Some indole compounds were found to be increased in blood and urine of tuberculous patients[7] and animals[8]. These were namely serum total indoles, blood serotonin and indole acetic acid[7][8]. This out-come increase in indole derivatives in tuberculosis lead Abdel Kader et al.[7] to propose a probable endogenous biochemical defense mechanism against the invading mycobacterium in tuberculosis. Also Stepanian[19][20] and Maslennikova[17] recorded increased serotonin level in patients with advanced tuberculosis. Kulybko[16] anyhow found diminished serotonin and increased histamine level in acute primary tuberculosis in children.

One might raise the possibility that the tissues of tuberculous patients are equipped with active biochemical defense mechanisms against T.B. organisms based on the production of indole and imidazole derivatives which proved to be highly tuberculostatic both in vitro and in vivo.

Histamine and serotonin have been settled as endogenous biochemical elements in allergy[14][21][16]. The storage sites of serotonin proved to be the platelets which are necessary for the production of fibrosis. Both allergy (Koch phenomenon and lymphocytic infiltration) and fibrosis do participate in the body mechanisms against tuberculosis[14][21].

Considering the function of both, histamine and serotonin as chemical mediators and transmitters[12], one might postulate that both heterocyclic amines represent also endogenous biochemical defense agents against tuberculosis; histamine taking a more active role in early T.B. while serotonin might participate in advanced cases. Besides it is a well known fact that asthma is rarely complicated with tuberculosis[11]; it only occurs as a complication to cortisone therapy. This might be due to the simple reason that histamine is one of the main endogenous allergic mediators participating in genesis of asthma. This is an additive proof of the antituberculous effect of histamine.

References

1) Abdel Kader, M. M. and Zaki, O.: Exper., 14: 455, 1958.
2) Abdel Kader, M. M. and Zaki, O.: Jap. J. Tuberc., 8(1), 1, 1959.
3) Abdel Kader, M. M. and Zaki, O.: Jap. J. Tuberc., 8(2–4), 106, 1960.
4) Abdel Kader, M. M. and Zaki, O.: Exper., 16: 140, 1960.
5) Abdel Kader, M. M. and Zaki, O., Hasaballa & Shehata, H.: Jap. J. Tuberc., 8: 106, 1960.
6) Abdel Kader, M. M. and Zaki, O.: Jap. J. Tuberc., 9(2–4), 65, 1961.
7) Abdel Kader, M. M., Abou El Waffa, M. H., Abdel Aziz, M. T., Soffora, A. M., Soliman, K. M., Fahmy, K. and Sallam, N.: Kekkaku, 52: 243, 1977.
8) Abdel Kader, M. M., Abdel Aziz, T. A., Soliman, K. M., Tawdrous, G. and Sallam, N.: Kekkaku, 52: 295, 1977.
9) Abdel Kader, M. M., Soliman, K. M., Shouab, S. and El-Moursi: Kekkaku, 52: 327, 1977.
10) Abdel Kader, M. M., Soliman, K. M., Elian, S., Shouab, S., El-Moursi, B. A. and Halawa, F.: Kekkaku, 53: 499, 1978.
11) Earle, B. Weiss, Maurice, S.(ed.): Bronchial sathma. Mechanisms and Therapeutic title, Brown and Company, Boston, 1976.
12) Donald, B., Tower: The nervous system basic sciences. Boven Press. New York, 1975.
13) Feldman, W. H. and Hinshaw, H. C.: Am. Rev. Tuberc., 51: 582, 1945.
14) Goodman, L. and Gilman, A., Pharmacological Basis of Therapeutics. Collier Mc Millan London–Toronto, 1970.
15) Kahlson and Rosengreen(1968) in Pharmacological Basies of Therapeutics. Goodman L. S. and Gilman A. Collie Mc Millan London, 1970.
16) Kalybko, O. M. and Sereda E. V.: Pediatrya, 4: 12, 1967.
17) Maslennikova, N. K.: Probl. Tuberk., 51: 26, 1973.
18) Michael E. Miller: Ped. Clinics of North America, 24–2–1977.
19) Stepanian, E. S.: Vrach Delo, 10, 56 Oct. 1966.
20) Stepanian E. S.: Probl. Tuberk., 45: 59, 1967.
21) Topley and Wilson: Principles of Bacteriology Virology and Immunity 6th. Ed. Sir Giraham, Sir Ashly, Sir Wilson. Edward Arnold, 1974.
22) Well, H. G. De Witt and E. R. Long: The Chemistry of Tuberculosis. Williams & Wilkins. Baltimore (1923), p. 252.