Histoplasmosis: Treatment of Two Cases with Beta-diethylaminoethyl Fencholate

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The antifungal agent, Beta-diethylaminoethyl fencholate has been demonstrated to inhibit the cultural growth of various fungi including Histoplasma capsulatum. Animals of several species have been subjected to acute and chronic toxicity studies with results that implied adequate safety to warrant clinical trial.1

The purpose of this report is to relate our recent experience with Beta-diethylaminoethyl fencholate in the treatment of two patients suffering from histoplasmosis. From Dr. Mackinnon Ellis, we first learned of this new drug, which he was employing in a case of histoplasmosis.2 There has also been a report of its clinical trial by Michael and Vogel3 who started the drug in their case several days after the development of clinical and radiographic improvement. They were unable to assess its usefulness.

Because of the relative paucity of cases of active histoplasmosis coming under the observation of any investigator and because the natural course of the disease is unknown, the evaluation of the usefulness of any drug in the treatment of histoplasmosis is difficult. Nevertheless, it is hoped that this report will contribute to an appraisal of the suitability of Beta-diethylaminoethyl fencholate in the treatment of histoplasmosis, and will stimulate further study by those who may encounter this uncommon disease.

Chronic Pulmonary Histoplasmosis

Case 1: R. No. 55019. A 63 year old white Tennessee farmer was first admitted to the Thayer Veterans Administration Hospital, Nashville, Tennessee on April 27, 1953. He had been well and working until the onset about three months previously of weakness, anorexia, slight nausea, night sweats, and chronic productive cough. His weight had dropped from 145 to 115 pounds. Extensive diagnostic studies failed to disclose any disease process. He was discharged May 22, 1953, unimproved, with nonspecific supportive medication.

On readmission February 26, 1954, his symptoms were essentially the same. His weight had not changed. His cough was productive of about 150 cc. sputum daily of which some 30-40 cc. were thick purulent secretions. On examination he appeared chronically ill, thin and tired. Dental status was poor. Auscultation of the chest disclosed moist medium-sized rales at the left apex posteriorly and rhonchi over both upper fields. The spleen and liver were not palpable. There was neither local nor generalized glandular adenopathy. There were no oral or lingual ulcers and the skin was not remarkable.

Initial laboratory findings were as follows: white blood cell count, 9,750; polymorphonuclear leukocytes, 80 per cent; lymphocytes, 19 per cent, eosinophils, 1 per cent. Sedimentation rate 34 mm, in 1 hour (Wintrobe corrected). Hematocrit was 41 mm. The urine concentrated to a specific gravity of 1.021; albumin and sugar were not present; microscopic examination was negative. Serum proteins were 6.6 grams per cent with

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albumin and globulin each being 3.3 grams per cent. In early March, 1954, skin tests to tuberculin (PPD Nos. 1 and 2) and to blastomycin undiluted* were negative. A barely positive reaction to coccidioidin, 1:100* and a positive reaction, measuring 10 mm. induration and 12 mm. erythema, to histoplasmin, 1:100,** were demonstrated. A second test with PPD No. 2 on March 16, was negative. Ten sputum smears and cultures were negative for acid fast bacilli. Two sputum cultures obtained March 22, and a third culture obtained March 24, were reported positive for Histoplasma capsulatum. Blood and bone marrow fungus cultures were negative. Bronchoscopic washings from the right and left upper lobe bronchi were negative on culture for fungi. The blood sera of March 25, and 30, showed a 1:16 reaction in the complement fixation test.

Chest roentgenograms (Figure 1A) on the previous admission of May, 1953, had shown only thickening of the pleura and several subpleural blebs at the right apex. By the second admission, March, 1954 (Figure 1B) there had developed bilateral infiltration interpreted as productive inflammatory disease extending from the apices to the second anterior interspace with linear strands radiating from the hilar regions to the apices. A radiolucent area at the right apex had persisted without change and on planographic study this appeared probably to be an emphysematous bleb.

Electrocardiogram showed occasional premature ventricular contractions and a first degree heart block, the P-R interval varying between 0.22 and 0.24 seconds.

His clinical course has been observed 13 months during which period there has been

* Blastomycin was kindly supplied by Dr. David T. Smith, Durham, N. C.
* Coccidioidin was kindly supplied by Dr. Charles E. Smith, San Francisco, California.
** Histoplasmin, Eli Lilly.
both clinical and roentgenographic improvement. His treatment may be conveniently separated into three phases, consisting of three months of strict bed rest, two months of bed rest supplemented by treatment with Beta-diethylaminoethyl fencholate and eight months of gradually increasing activity.

Treatment during the first three months (March-May 1954) consisted of 24 hours rest in bed each day, a full diet, and general measures which included removal of all teeth for chronic gingivitis and periodontoclasia. His symptoms persisted and in addition he developed mild peripheral neuritis thought to be secondary to poor nutritional status. This slowly improved on a full diet with vitamin supplements. Night sweats gradually disappeared, but little improvement was noted in the anorexia, weakness, cough or weight. The chest roentgenogram of April 21 (Figure 1C) indicated increase of disease during the first two months but improvement was evidenced by the end of the third month, May 24 (Figure 1D).

During the next two months (June and July, 1954) his rest program was unaltered and he received Beta-diethylaminoethyl fencholate (MRD-112). This medication,* furnished in ampules containing 150 mg. of the drug in alcohol, was administered by diluting the contents of an ampule in 200 ml. of physiological saline and infusing by slow intravenous drip once daily. The same antecubital vein was used each day with occasional exceptions for 60 days without encountering thrombosis or phlebitis. The clinical and roentgenographic evidence of improvement, which had started during the month (Figure 1D) prior to drug treatment, continued. Cough, sputum production and muscular aching decreased. Appetite improved. He gained weight from 115 to 126 pounds and remained afebrile. Chest roentgenogram of July 26 (Figure 2E) showed improvement evidenced by gradual regression and contraction of the densities in both apices.

The post medication period of eight months, August, 1954, through March, 1955, has been characterized by continued clinical and roentgenological improvement. He remained in the hospital until December, 1954, during which time he was allowed increased activity; resting two hours before bed, and two hours in the afternoon and nine hours at night. His appetite returned to normal, he gained an additional eight pounds, and his cough lessened. Considerable lassitude persisted.

He was then at home from January, 1955, until the present (April, 1956) during which time he spent eight hours daily in bed, eight hours in a chair, and eight hours doing light farm chores—milking a cow, feeding hogs and chickens. He noted an increase in energy, and a decrease in cough was significant, being productive of only 4 to 5 cc. of mucoid sputum daily. There was some decrease in appetite, however he stated he forced himself to eat, and he gained another two pounds.

Serial chest roentgenograms following completion of drugs showed the most marked regression of densities attributed to inflammatory infiltration in both upper lung fields through September 1, 1954 (Figure 2F) with gradual but steady clearing continuing through December, 1954 (Figure 2G) and March, 1955 (Figure 2H).

Repeated sputum cultures for Histoplasma capsulatum were consistently overgrown with contaminants which is the rule in our laboratory in the warmer months. Seven uncontaminated cultures were negative for fungus growth. Repeated smears and cultures of sputum were negative for acid fast bacilli. The monthly complement fixation antibodies varied little until November, 1954, when they declined to 1:2. In December, 1954, this test was recorded as negative; and in March, 1955, as 1:8. Complement fixation tests were done in the U. S. Public Health Laboratory, Chamblee, Ga. from March, 1954, through July, 1954, employing the technique of Schubert et al.; in the Veterans Administration Area Reference Laboratory, Atlanta, Ga. in August and September, 1954, by the technique of Norden; and subsequently at the Army Medical Center, Washington, D. C. by the technique described by Campbell et al.14

Toxicity studies, done before and after the use of Beta-diethylaminoethyl fencholate, consisting of clinical observation, hematological examinations, and renal and hepatic function tests, demonstrated no significant deviations from normal. The WBC, differential counts and hematocrit disclosed no hematopoetic alterations; urinalysis, NPN and PSP tests revealed no suggestion of renal irritation; bromsulphalein, cephalin flocculation, thymol turbidity, serum bilirubin, alkaline phosphatase and serum protein determinations remained normal.

Disseminated Histoplasmosis

Case 2: R. No. 40338. A 54 year old retired South Carolina truck farmer was referred to Thayer Veterans Administration Hospital in August, 1950, for further treatment of adenocarcinoma of the thyroid gland, for which a right hemithyroidectomy had been done elsewhere. He also had had diabetes mellitus. Shortly after admission to this hospital total thyroidectomy was done. No local lymph node was found at

*Kindly supplied by the William S. Merrill Company, Cincinnati, Ohio.
operation. Microscopic sections of the excised thyroid gland showed evidence of malignancy. His postoperative course was uneventful and he returned home on a small dose of thyroid extract and 15 units of protamine zinc insulin daily. Subsequent examinations from 1950 to 1953 showed no evidence of recurrence or metastases.

He was readmitted in January, 1954, because of the discovery of two small nodules over the right sternoclavicular joint. A radical neck dissection and mediastinal exploration of January 18, 1954, revealed only two small lymph nodes which microscopically showed metastatic cancer. The postoperative course was stormy primarily because there developed around the tracheotomy tube a persistent infection which resulted in a superior mediastinal sinus tract which drained moderate amounts of serosanguinous fluid. By June, 1954, he had improved so he was ambulatory within the hospital.

In July, 1954, he became worse and thereafter pursued a steady downhill course. He developed septic fever reaching 102° F., ascites, mild jaundice, splenomegaly and hepatomegaly. A rash appeared, characterized by discrete, small tawny papules, located on the upper arms and the anterior and posterior aspects of the chest. The total white blood cell count was 2,000; with a differential showing 50 per cent polymorphonuclear leukocytes and 50 per cent lymphocytes. Biopsies of the bone marrow obtained from the iliac crest and of a dermal papule revealed intracellular yeast-like bodies morphologically typical of Histoplasma capsulatum.

On July 21, 1954, when he was critically ill, Beta-diethylaminoethyl fencholate, 150 mg. in 150 cc. physiological saline was given intravenously and this was repeated each day until July 26, the day of death. No improvement was apparent.

FIGURE 2
Laboratory studies just prior to therapy disclosed: white blood cells, 2,500; polymorphonuclear leukocytes, 79 per cent; lymphocytes, 21 per cent; hematocrit, 31 mm.; total serum proteins, 5.1 gm. per cent with albumin 3.0 gm. per cent and globulin 2.1 gm. per cent. The cephalin flocculation was 4 plus; thymol turbidity, 3.0. The indirect Van den Bergh was 1.2 mg. per cent and the total serum bilirubin, 2.2 mg. per cent. The NPN was 67 mg. per cent. Urinalysis showed a trace of albumin, 2-3 red blood cells, occasional white blood cells, and a few granular casts. On the day of death, the white blood cell count was 7,500 with 93 per cent polymorphonuclear leukocytes and 7 per cent lymphocytes.

Histoplasma capsulatum was cultured from specimens of blood and bone marrow obtained on July 21, and 22, respectively. The blood serum of July 23, gave a 1:128 complement fixation reaction for Histoplasma.

Post-mortem examination showed widespread disseminated histoplasmosis. The only evidence of adenocarcinoma was found in one mediastinal lymph node, in which there were also numerous organisms of histoplasmosis.

Discussion

Except for ethyl vanillate, which gave some encouraging results in a small group of patients studied by Christie and Peterson,9 no drug of promise has so far been employed satisfactorily in the treatment of histoplasmosis. Beta-diethylaminoethyl fencholate is a new chemotherapeutic agent which we have tried in two cases of culturally proved histoplasmosis.

In the first patient with chronic pulmonary histoplasmosis, our observations do not conclusively demonstrate that this drug altered the course of the disease. There are a number of reasons why the evaluation is difficult. There is too little known about the natural course of pulmonary histoplasmosis to say that the illness of this patient was milder or shorter than the average. In this respect the problem is not like that in pulmonary tuberculosis where extensive clinical experience has established the natural course of untreated infection; yet even in tuberculosis, correct evaluation of specific antimicrobial agents has been difficult. Furthermore, bearing in mind that Johnson and Batson9 noted a favorable response to bed rest and general measures in their case of pulmonary cavitary histoplasmosis, it is impossible to show to what extent his recovery was the result of bed rest and general therapeutic measures instead of specific drug effect. Clinical and roentgenographic improvement was evident prior to specific drug treatment. The gradual improvement continued during drug therapy and thereafter, both during the phase of bed rest and the period of rehabilitation. Nevertheless, the possibility exists that Beta-diethylaminoethyl fencholate did favorably affect his course. The dosage and duration of administration of the drug were selected arbitrarily and may not have been optimum.

In the second patient, it was evident that the few days of drug treatment did not alter the rapid downhill course of his disease. If this drug has any suppressive effect on histoplasmosis in the human, it was not sufficiently potent to influence this particularly overwhelming disseminated infection.

REFERENCES