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METHOD OF TREATING RHEUMATOID ARTHRITIS WITH HISTIDINE

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ABSTRACT OF THE DISCLOSURE

The administration of the amino acid histidine or non-toxic salts of that acid is useful in the alleviation of symptoms and effects related to rheumatoid arthritis.

The invention described herein was made in the course of, or under, a grant from the U.S. Public Health Service, Department of Health, Education, and Welfare.

This invention relates to a method for relieving symptoms and effects associated with rheumatoid arthritis. More particularly, this invention is concerned with a method of relieving such symptoms and effects by the administration of effective dosages of histidine or non-toxic histidine salts.

Histidine (also known as alpha-amino-4(or 5)-imidazolepropionic acid or glyoxaline-5-alanine) and its derivatives are known in the art. Histidine hydrochloride, in particular, has been employed as a therapeutic agent for the treatment of peptic ulcers although it is no longer recommended for that purpose.

It has now been discovered that the use of histidine or non-toxic salts of histidine, preferably L-histidine, L-histidine monohydrochloride monohydrate or compositions containing these compounds as active ingredients are effective in the treatment of rheumatoid arthritis. The treatment of patients with these compositions results in the alleviation of any or all of the manifestations of this disease including pain, tenderness, stiffness, swelling, redness, warmth, deformity and limitation of motion of any and all joints characteristically involved in this condition. In addition the administration of histidine and its derivatives also results in a lessening of fatigue, fever, malaise, anorexia, weight loss, muscle atrophy, anemia, abnormality of the erythrocyte sedimentation rate, concentration of rheumatoid factor in the blood, and other manifestations of rheumatoid arthritis.

The compositions of this invention may be prepared in any manner known in the art. For example, it may be produced by isolation from protein hydrolysates. It will be understood by those persons skilled in the art that the histidine compounds employed in the novel treatment of this invention may be combined with any compatible pharmaceutical carrier or vehicle and, in addition, can be combined with other compatible active compounds such as analgesics and anti-inflammatory substances.

The preferred method of treatment with the histidine compounds disclosed herein comprises the oral administration of the compound in amounts ranging from 0.375 to 8.0 grams or more per day, preferably 4.0 grams/day. The dosage may vary widely within this range depending upon such facts as the size of the patient and the severity of the patient's condition. The number, amount and timing of daily dosages is not critical and up to 5.0 grams of the active ingredient may be given at one time, although spaced, smaller dosages are preferred. Moreover there is no apparent limit to the duration of treatment by this method.

The administration of the composition is susceptible to any one of the conventional pharmaceutical forms such as tablets, dragées, gelatin-coated pills and preferably gelatin capsules. It may also be formulated in liquid form.

For convenience, individual doses containing 100 to 500 mg. of active substance are preferred. Although oral administration is preferred, the active ingredient used in the treatment may also be dispensed as a suppository or as a sterile injectible liquid in similar individual doses.

The efficacy of the treatment of the invention has been determined clinically in a study performed on 9 men and 50 women with definite or classical rheumatoid arthritis. The patients had an average age of 51 years and the average duration of the disease was 8 years. Rheumatoid factor was present in 89% of the patients.

Prior to actual treatment with the histidine compositions, each patient was treated for a varying period of time with a placebo. Placebo capsules contained Cream of Rice cereal. Patients were not advised when the placebo period ended in order to prevent the psychological effect of treatment from interfering with the evaluation. Half of the patients received placebo for at least 4 months and a histidine composition for at least 6 months. Eight patients received placebo for 11 months, and 13 patients have so far received histidine for 10 months. The length of the placebo period was not uniform primarily because the placebo period elected was one month when the study began, then increased to 4 months, and then to 6 months in some and 12 months in others when it became apparent that a longer placebo period would give more credibility to the results.

The length of the treatment period was not uniform because the study is ongoing and the patients did not all begin taking histidine at the same time. Treatment comprised oral administration of L-histidine or L-histidine monohydrochloride monohydrate in 375 milligram capsules, taken 1 to 4 at a time, at regular intervals throughout the day in a daily dose of 1 to 8 grams. The average dose was 3 grams/day.

During both the placebo and actual treatment periods, patients were evaluated at two to three week intervals and the following information was obtained on each evaluation:

(a) Time of day;
(b) Dose of either histidine or placebo taken by determining number of capsules given and number remaining;
(c) Grip strength—taken three times in each hand with a mercury manometer and standard bandage blood pressure cuff, folded according to the procedure used by the Cooperating Clinics Committee of the American Rheumatism Association and inflated to 20 mm. Hg;
(d) Time to walk 25 feet and 50 feet;
(e) Duration of morning stiffness;
(f) Dose of aspirin, prednisone, Darvon and any other drugs taken by the patient;
(g) Assessment of patient's general status as reported by the patient.

At one to two month intervals, blood was obtained for Westergren erythrocyte sedimentation rate, hematocrit, and serum histidine; serum remaining was stored at —20° C. White blood count, liver and kidney function tests, serum albumin and globulin, serum cholesterol, blood sugar, other blood tests and urinalysis were done at less frequent intervals.

During the study, patients and the other physicians caring for the patient were allowed to change the patient's therapy (other than administration of histidine) as they thought fit, based on the patient's condition. During the placebo period that preceded the administration of histidine, the patients took the following drugs (average dose): aspirin, 2.4 gm./day (three patients took no aspirin); prednisone, 9.7 mg./day in 24 patients; dextropropoxyphene (Darvon), 182 mg./day in 24 patients; phenylbutazone, 100 mg./day in 1 patient; indomethacin,

52 mg./day in 5 patients, and maintenance gold in 1 patient. No patients received chloroquine or immunosuppressive agents.

The information obtained from all the patients in the study was pooled and statistically evaluated. For each month of the placebo period, no grip, walk, or sedimentation rate was statistically significantly different from the corresponding value at the end of the placebo period. During the histidine period, however, the results were quite different. For every month of the histidine period, the values for grip strength, walking time, and the sedimentation rate were all statistically significantly better than the corresponding values obtained at the end of the placebo period.

During the 11-month placebo period, there was a slight but statistically significant deterioration in grip strength but no consistent trend in walking time or sedimentation rate. During the period of histidine administration not only was improvement apparent but the degree of improvement was statistically significantly correlated with the month of therapy, the maximum improvement occurring at the end of the histidine period. After 10 months of histidine administration, the grip strength was 30 mm. Hg stronger, the walking speed was 6 seconds per 50 feet faster, and the sedimentation rate was 18 mm. (Westergren) lower than the mean value for the placebo period.

In 25 patients, less aspirin was required during histidine administration than during the placebo period. In these 25 patients, the average decrease in the dose of aspirin was 1.6 grams per day. Three patients required more aspirin after histidine; in each, the increase was 0.3 gram per day. In all the other patients, the aspirin dose did not change. Six of the 24 patients receiving prednisone required less of this drug after histidine; the average decrease in dose was 4 milligrams per day; no patient required more prednisone. Six patients reduced their dose of Darvon after histidine; the average decrease in dose was 65 milligrams per day; no patient increased the dose. The one patient receiving phenylbutazone discontinued this drug after histidine treatment. One patient reduced the dose of indomethacin from 150 milligrams per day to zero; one patient took indomethacin (25 milligrams per day) only during the histidine period; and in 4 patients the dose of indocin remained unchanged. No other changes in the dose of anti-inflammatory drugs took place during the study, nor was there any change in any patient in physical therapy during the study. Thus, it does not appear that the improvement noted during the histidine period of this study was due to any increase in the dose of any anti-inflammatory drug except histidine. On the contrary, improvement appears to have taken place in spite of a significant reduction in the dosage of other drugs.

Anemia (i.e. hematocrit less than 37% in a woman or less than 40% in a man) was noted in 15 patients before histidine treatment, but in only 1 patient after histidine treatment. Morning stiffness decreased in 25 patients and increased in 4 patients after treatment with histidine; in the remaining patients there was no change in morning stiffness.

In 23 patients, placebo was given after the patients had finished a course of histidine therapy. Nineteen of these 23 patients showed evidence of deterioration in one

or more of the parameters measured, i.e. grip, walk, and sedimentation rate. In those patients that showed deterioration, the average period of time between the cessation of histidine therapy and the onset of deterioration was 5 months.

Table 1 compares the results obtained after the administration of histidine for six months with the results obtained after an equal period of placebo, gold or hydroxychloroquine as noted in three other studies, a gold study by the Cooperating Clinics Committee of the American Rheumatism Association, a hydroxychloroquine study by the same group; and a gold study by the Empire Rheumatism Council. The results obtained with histidine are significantly better than the results obtained with placebo in all three studies and approximately equal to the results obtained with gold in the two gold studies. The improvement found with histidine administration appears to be somewhat better than the improvement found with hydroxychloroquine.

TABLE 1.—COMPARISON OF HISTIDINE WITH OTHER DRUGS

Treatment (6 months)	Grip (mm. Hg)	Walk (sec./50 ft.)	ESR (Westergren)
Histidine (± S.E.)	29±6.9	3.5±1.4	13±3.7
Placebo (American Rheumatism Association)	12	0	1
Do	13	1.2	1
Placebo (Empire Rheumatism Council)	9	(1)	5
Gold (American Ruhematism Association)	26	2.0	20
Gold (Empire Rheumatism Council)	37	(1)	21
Hydroxychloroquine (American Rheumatism Association)	29	0	7

[1] Not done.

No side effects of histidine were observed at any time throughout this study. Specifically, patients did not complain of the taste of the histidine, nausea, diarrhea, epigastric discomfort or anorexia and developed no rashes, abnormalities of renal or hepatic function, anemia or leukopenia, that could be attributed to the administration of histidine.

The results of the clinical studies clearly establish that the administration of histidine is effective in alleviating symptoms of rheumatoid arthritis.

What is claimed is:

1. A method of treating symptoms and effects of rheumatoid arthritis in humans comprising the human ingestion of a compound selected from the group consisting of histidine and a nontoxic salt of histidine in an amount sufficient to alleviate said symptoms.

2. The method of claim **1** wherein said compound is L-histidine.

3. The method of claim **1** wherein said compound is L-histidine monohydrochloride monohydrate.

4. The method of claim **1** wherein the daily amount of ingestion of said compound is 0.375 to 8.0 grams.

5. The method of claim **1** wherein said compound is orally ingested.

References Cited

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