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3,705,946

METHOD OF TREATING HYPERURICEMIA

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No Drawing. Filed May 25, 1971, Ser. No. 146,817

Int. Cl. A61k 27/00

U.S. Cl. 424-279

3 Claims

ABSTRACT OF THE DISCLOSURE

Mycophenolic acid employed in the treatment of hyperuricemia.

BACKGROUND OF THE INVENTION

Man, unlike most other mammals, excretes uric acid as an end-product of purine metabolism. In humans impairment of the ability to clear uric acid, or an increase in purine catabolism, or an excessive dietary intake of purines, results in hyperuricemia, an increase of circulating uric acid. Hyperuricemia can result in the deposition of uric acid crystals in any tissue of the body, but particularly in the cartilage of joints, bone and kidney. The condition in which uric acid crystals are deposited in any tissue is known as gout.

There are several therapeutic treatments for the alleviation of hyperuricemia and thus the prevention and/or dissolution of uric acid deposits in tissue. For example, colchicine, phenylbutazone and indomethacin are employed in the treatment of acute attacks of gout. Phenylbutazone has the ability to decrease the tissue and serum levels of uric acid. The administration of all three compounds, however, is accomplished by undesirable side-effects including gastrointestinal spasm, headache and bone marrow depression. Another method of treatment involves the use of uricosuric agents which increase the excretion of uric acid in part by decreasing the reabsorption of uric acid in the kidney via inhibition of tubular transport system. Probenecid and sulfinpyrazone are useful drugs employed in this manner. Again, both produce, as a side effect, some gastric intolerance and even peptic ulcer. Finally, allopurinol is used in a hypouricemic agent and acts by decreasing the circulating level of uric acid by inhibiting the enzyme, xanthine oxidase. This enzyme catalyzes the conversion of xanthine and hypoxanthine into uric acid. Allopurinol administration can also be accompanied by certain undesirable side-effects including leukopenia, epigastric distress and skin reactions. Further, allopurinol may be incorporated into RNA or DNA genetic material.

It is an object of this invention to provide a method of reducing the serum uric acid concentration in humans by employing an agent which is relatively free from undesirable side-effects.

SUMMARY

In fulfillment of the above and other objects, this invention provides a method for the reduction of uric acid levels in humans by administration of from 200-5000 mg. per day of mycophenolic acid or an alkali metal salt thereof; either in the form of the free acid or when the salt is used in an amount equivalent to 200-5000 mg. per day of the free acid. Among the useful alkali metal salts are the sodium and potassium salts. For oral administration, either the salt or free acid may be employed. With parenteral administration (intravenous, intramuscular, etc.) an alkali metal salt of mycophenolic acid is customarily employed.

An illustration of the process of this invention follows: A patient suffering from adenocarcinoma of the breast received intravenously 200 mg. of the sodium salt of

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mycophenolic acid on day 1 and 400 mg. on day 2. On day 4 the patient received 400 mg. of sodium mycophenolate by the intramuscular route three times a day. At the end of that week the dosage was increased to 400 mg. intramuscularly 4 times a day, and this regimen was continued for about six weeks. After a hiatus of one month, during which time other therapy was instituted, mycophenolic acid administration was continued with the patient being given 400 mg. orally four times a day for a period of about three weeks. The dosage was then increased to 600 mg., four times a day, by the oral route and she was continued on this dosage for another two weeks.

At the time of initiation of mycophenolic acid therapy the patient's serum uric acid level was 10.6 mg. percent. At the end of the first two weeks of the above therapeutic procedure, the uric acid level had dropped to 9 mg. percent. By the time the initial therapeutic course was discontinued, the patient's serum uric acid level had dropped to 3.7 mg. percent. When mycophenolic acid treatment was reinstituted, the patient's serum uric acid level was at an 11.6 mg. percent level. The second course of treatment yielded another decrease in circulating uric acid level with a drop to 5.0 mg. percent at the time the treatment with mycophenolic acid was terminated.

In summary, the above patient showed a progressive decrease in uric acid levels from a somewhat elevated level to a normal level during two courses of treatment; one with sodium mycophenolate and the other with mycophenolic acid. The total amount of mycophenolic acid given varied from 200 mg. per day to 2400 mg. per day.

Mycophenolic acid is a relatively non-toxic substance. Table 1, below, summarizes toxicity data on this compound, obtained to date.

TABLE 1.—ACUTE TOXICITY

Species	Route	Compound	LD ₅₀ , mg./kg.
Mice.....	Oral.....	Sodium mycophenolate.....	1,176-1,600
Do.....	do.....	Mycophenolic acid.....	1,685-2,150
Rats.....	do.....	Sodium mycophenolate.....	387-418
Do.....	do.....	Mycophenolic acid.....	416-488
Mice (male).....	Intravenous.....	Sodium mycophenolate.....	455-541
Mice (female).....	do.....	do.....	434-507
Rats (male).....	do.....	do.....	405±20
Rats (female).....	do.....	do.....	427±18

FORMULATIONS

In administering mycophenolic acid or an alkali metal salt thereof, such as the sodium salt, to humans, a parenteral route of administration may be employed. For example, ampoules for use in intravenous or intramuscular injection, can be prepared containing 214 mg. of sodium mycophenolate (equivalent to 200 mg. of mycophenolic acid), 5 mg. of phenol and 2 ml. of water. Similarly, ampoules containing 600 mg. of sodium mycophenolate, 0.4 ml. of ethanol, 0.042 mg. of benzyl alcohol, 10 mg. of phenol, 14 mg. of monobasic potassium phosphate, 10 mg. of sodium citrate, and 4 ml. of water can be used. (The pH of this solution is adjusted, if necessary, to pH=7 by the addition of acid or base, as required prior to placing in ampoules.) For oral administration, the compounds are preferably administered in telescoping gelatin capsules, each capsule containing 250 mg. of mycophenolic acid and up to 700 mg. of talc, or silica gel, or starch, or microcrystalline cellulose singly or in combination, up to 20 mg. of magnesium stearate and up to 50 mg. of stearic acid. If sodium mycophenolate is employed, the ingredients are the same except that talc in an amount of no more than 125 mg. can be used. Specifically, ampoules containing 200 mg. of mycophenolic acid and 500 mg. of starch, thoroughly mixed, constitute a useful medicament.

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We claim:

1. The method of reducing the uric acid level in humans which comprises administering to a human having an elevated uric acid level, from 200 to 5,000 mg. per day of mycophenolic acid, or the sodium or potassium salt thereof.

2. The process of claim 1, wherein the therapeutic agent is administered by the oral route.

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3. The process of claim 1, wherein the therapeutic agent is administered by the parenteral route.

References Cited

5 American Druggist, May 19, 1969, pp. 33-34.

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