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2,935,448

PHOSPHATIDE THERAPEUTIC COMPOSITION AND METHOD OF TREATMENT THEREWITH

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No Drawing. Application February 25, 1959
Serial No. 795,364

7 Claims. (Cl. 167—65)

This invention relates to medicinal compositions useful for treating osteoarthritis and to a process of treating humans having osteoarthritis. More particularly, this invention relates to such compositions in which the active ingredient is the acetone-insoluble fractions of phosphatides of corn or maize and to the method of controlling osteoarthritis in humans with such compositions.

The disorder, osteoarthritis, is known by a number of synonyms, including hypertrophic arthritis, degenerative joint disease, senescent arthritis, degenerative arthritis, and arthritis deformans. It is a chronic disabling disease affecting at least twenty-five million people in this country, of whom more than a million are so badly afflicted as to require medical attention in any given year.

The pathological and clinical features of the disease are well described in standard textbooks of medicine and arthritis. The process begins with degeneration of articular cartilage, the normal function of which is to cushion the ends of bones where they come together as a joint. Subsequently a series of secondary changes occur which are reparative and compensatory in nature. These changes include hypertrophy and increased vascularity in the surrounding fibrous or periarticular structures; increase in number and size of the villi of the synovial membrane, which may contain cartilage, may be partially ossified, or may even break off to form loose bodies ("joint mice") in the joint; and, ultimately, complete destruction of the articular cartilages, with exposure of the underlying bone, which becomes very dense, polished and hard or eburnated.

The disease may attack any joint or joints. Those subject to frequent use; such as, for example, the fingers; or to weight: such as, for example, the spine, hips and knees are most commonly involved. It frequently affects the terminal joints of the fingers, especially in women after the menopause, and the enlargement so produced is known as Heberden's nodes.

The basic cause of the degeneration of articular cartilage identified as osteoarthritis is unknown in most cases. In some instances, antecedent destructive factors may be obvious; such as, for example, acute or chronic occupational or postural traumata, and previous inflammatory or infectious processes, such as rheumatoid, gouty or suppurative arthritis. Such cases have been appropriately classified as, secondary osteoarthritis. But, in the great majority of cases, the reason for the deterioration of these articular cartilages is completely obscure and such cases are classified as primary osteoarthritis. Observant physicians have long suspected that the disease is associated with a predisposing hereditary factor, and Stecher and his associates, by statistical analyses, have demonstrated a familial tendency to the development of this type of rheumatism, at least insofar as the incidence of Heberden's nodes is concerned. Even granted that such an hereditary vulnerability of articular cartilage exists, the actual precipitating cause or causes of the destructive changes remain unknown. Other work in this

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field which is exemplary was that of Wollenberg, who has shown experimentally that interference with the circulation to the joint is followed by hypertrophy of bone. Pemberton and associates confirmed and extended this finding. Such observations have not, however, led to any recognized treatment of the disease.

Heretofore, no specific treatment for osteoarthritis was available, with the exception, in recent years, of therapy involving the use of cortisone and its derivatives or analogues. While a symptomatic improvement in the treatment of this disease with such drugs has been noted, the latter preparations provoke so many deleterious side effects, particularly in the aged, that their use is not recommended except by intra-articular injection. Prior to the foregoing therapy, the therapeutic efforts in the treatment of the disease have been limited to the prevention of postural trauma by weight reduction, correction of obvious deformities by orthopedic procedures, improvement of mobility of joints by physiotherapy, and relief of pain by analgesics. In the latter therapy, phenylbutazone (3,5-dioxo-1,2-diphenyl-4-n-butyl pyrazolidine) is the most effective analgesic employed, but it is too toxic to permit prolonged administration.

The lack of therapeutic compositions for treating osteoarthritis which are non-toxic and which do not produce deleterious side effects is overcome by this invention which is based on the discovery that the disease may be effectively treated with a therapeutic composition in which the active ingredient consists of the acetone-insoluble fractions of the phosphatides from corn or maize. More particularly, this invention is based upon the discovery that osteoarthritis may be effectively treated by administering a novel dosage unit form of the acetone-insoluble fractions of corn or maize phosphatides obtained by precipitation from corn or maize oil produced by hot or cold pressing of the seed of the grain.

The principal object of this invention is to provide non-toxic therapeutic compositions for treating osteoarthritis in humans to alleviate the pain in effected joints and to increase the motion, flexibility and mobility of such joints. Another object of this invention is to provide therapeutic compositions for treating osteoarthritis in humans wherein the active ingredient consists of the acetone-insoluble fractions of the phosphatides of corn or maize oil. A further object of this invention is to provide a novel dosage unit form of a therapeutic composition for treating osteoarthritis in humans wherein the active ingredient of the compositions consists of the acetone-insoluble fractions of phosphatides obtained by precipitation from corn or maize oil produced by hot or cold pressing of the seeds of such grain. Still another object of this invention is to provide a process of treating osteoarthritis in humans which comprises introducing, by oral administration, into the system of a human affected by the disease, a novel dosage unit form of a therapeutic composition containing as its active ingredient the acetone-insoluble fractions of phosphatides precipitated from corn or maize oil produced by hot or cold pressing of the seeds of such grains.

The phosphatides employed in this invention belong to a complex class of substances, the physiological function of which is largely a matter of speculation. Phosphatides are classed as compound lipides and are characterized by the fact that they invariably contain a phosphoric acid residue, fatty acids which vary according to the source of the phosphatides, one or more polyhydric alcohols; such as, for example, glycerol, sphingosine or inositol, and a nitrogenous moiety that is either basic or capable of functioning as a base; such as, for example, choline, aminoethyl alcohol or serine. Glycolipides, which are often associated in nature with the phosphatides, are also compound lipides, such as the cerebroside,

in which fatty acids, a carbohydrate, and a nitrogen compound are combined. Chemical investigation of these complex substances is so difficult that full details of their structure are lacking. They are of extreme importance since they are constituents of practically all living tissue and constitute a complex form of fat in such tissue. The phosphatides can be extracted and concentrated from vegetable and animal sources by virtue of the fact that they are insoluble in acetone.

The specific phosphatides employed in this invention are the corn phosphatides which are derived in a relatively crude form as a by-product of the commercial refining of corn oil by the process disclosed in United States Patent No. 2,150,732, granted March 14, 1939, to Benjamin H. Thurman, the entire disclosure of which patent is incorporated herein by reference. This process, briefly, consists of crushing the seed, removing the husks and pressing the residue to form a cake and obtain the oil. The oil may be filtered to remove fibrous materials and other solids present. It is then treated with a reagent for the purpose of precipitating the phosphatides which are then removed. The reagents employed to precipitate the phosphatides are water, alcohol, or aqueous solutions of acids, alkalis or salts. A full disclosure of this process for obtaining phosphatides from corn oil will be found in the above-identified patent.

The phosphatides of corn oil produced in the manner described above are known commercially as "wet gum." This wet gum contains almost all of the coloring matter of the crude oil and has a neutral corn oil content of about 50 percent by weight. There are a variety of commercial uses of this wet gum including the uses thereof as additives for chocolate and margarine which have been approved by the United States Food and Drug Administration. The wet gum is employed in this invention, preferably after it is further purified by extraction with acetone. The best mode contemplated for preparing the acetone-insoluble fractions of corn phosphatides for use in this invention is set forth in the following example:

Example I

The active ingredient employed in the compositions used in carrying out this invention is prepared from the phosphatides of corn or maize oil produced by the process disclosed in U.S. Patent No. 2,150,732. These crude phosphatides are referred to as wet gum and are known commercially under the trademark "Vodol." A porcelain receptacle containing about 5.5 liters of acetone is provided with a stirring device. About 1.6 kilograms of wet gum corn phosphatides (Vodol) is warmed to about 70° C. to increase its fluidity and then added slowly to the acetone with stirring. When the addition is completed, the stirring is continued for from about 10 to about 15 minutes. The suspension thus obtained is filtered through a Büchner funnel provided with a cloth filter sheet. The filtrate is collected and combined with those obtained from subsequent fractions in order that the acetone may be recovered by distillation for reuse. The precipitate obtained is transferred from the filter and is, again, slowly added with stirring to about 5.5 liters of fresh acetone. The stirring is continued for about 45 minutes after the addition of the precipitate is completed. The suspension obtained is filtered in the same manner as described above. The transfer of the precipitate and the extraction thereof in fresh acetone are repeated until a total of four extractions, excluding the first, are completed.

After the final extraction and filtration is completed, the precipitate is pressed in the filter to express as much acetone as possible from the precipitate. The precipitate is then transferred to a No. 10 sieve and forced therethrough to break-up the cake of precipitate. The lumps of the precipitate thus obtained are spread onto trays which are placed in a vacuum desiccator. The conduit between the desiccator and the vacuum pump is provided

with two Dry-Ice traps. The trays remain in the desiccator until the acetone is removed from the precipitate and the moisture content is reduced to below about 5 percent by weight; and, preferably below about 3 percent by weight. The dried material is then sieved through a No. 20 sieve.

The acetone-insoluble fractions of corn phosphatides obtained in the manner described above are a light yellow amorphous powder which is very hygroscopic and which oxidizes spontaneously on exposure to air at room temperature within a few days, turning brown at room temperatures. The hygroscopic property is overcome by adding about 2.0 percent by weight of commercial cornstarch to the powder. The tendency of the fractions to oxidize may be overcome by the addition thereto of small amounts of one of the standard anti-oxidants which are commercially available and which are used in the food industry. Alternatively, the powder may be stored in air-tight containers, capsules or packets under refrigeration at about 0° C. The acetone-insoluble fractions of corn phosphatides, when thus stored, retain their original appearance and therapeutic activity indefinitely. Stability tests conducted with samples stored in the foregoing manner have established that the samples may be preserved for as long as five years. These fractions, prepared as above, are of unknown constitution, but are known to contain a large percentage of lecithins and cephalins characteristic of corn phosphatides; and, as well, inositides, sterol glycosides and other unidentified carbohydrate substances.

The acetone-insoluble fractions of corn phosphatides employed in carrying out this invention may be associated with a carrier which may be either a solid or a sterile liquid. The compositions containing these active ingredients may take the form of capsules, powders, tablets or other dosage forms which are particularly useful for oral ingestion. Liquid diluents are employed in sterile condition for oral administration, and such a medium may be sterile water. The compositions may take the form of active material admixed with solid diluents and/or tableting adjuvants such as cornstarch, lactose, talc, stearic acid, magnesium stearate or gums. Any of the tableting materials used in pharmaceutical practice may be employed where there is no incompatibility with the acetone-insoluble fractions of corn phosphatides. When the compositions are employed in tablet form it is preferred that the tablets be coated with the standard disintegratable or reabsorbable coatings which seal the tablet from air and moisture. It is preferred to employ the therapeutic compositions containing the above active ingredient in the usual capsule of gelatin or other available materials used in capsules, which are orally administered in that form. These compositions may also be sealed in air and moisture resistant packets formed of heat-sealable synthetic resin sheets which may be opened when ready for administration and the contents orally ingested. Finally, the compositions may be introduced into sterile liquid vehicles and maintained in suspension therein by means of the usual surface-active agents employed for this purpose in the pharmaceutical art.

The dosage unit forms of the acetone-insoluble fractions of corn and maize phosphatides employed in carrying out this invention are compounded to provide for oral administration, on the average, of three cumulative, sequentially administered doses daily. The preferred total daily dosage of the above active ingredients is the equivalent, in an amount by weight, of about 1.0 percent by weight of the average daily total fat intake of the patient being treated. The total daily dosage of the active ingredient is preferably about 1.0 gram, but a total daily dosage may be in the range of from about 1.0 gram to about 2.0 grams, and as much as a total of 3.0 grams daily may be administered. A total daily dosage larger than 2.0 grams of the active ingredient may be employed, if desired, owing to the non-toxic properties of the active

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ingredient, but such larger dosages are unnecessary because the therapeutic efficiency of the treatment with these active ingredients is not enhanced thereby.

The preferred total daily dosage of the active ingredients of 1.0 gram and total daily dosage in the range of 1-2 grams of active ingredients is provided by the dosage unit forms; such as, for example, a capsule, tablet, packet or a measured amount of a suspension in a liquid. Each dosage unit form contains, preferably, about 0.3 gram of the acetone-insoluble fractions of corn or maize phosphatides prepared according to Example I. The dosage unit forms may contain the active ingredients in an amount in the range of from 0.3 to 0.6 gram, or larger individual doses may be administered simply by using more than one dosage unit form at a time. In the method of treating humans having osteoarthritis, according to this invention, it is preferred to administer, orally, No. 0 capsules which each contain about 0.3 gram of the acetone-insoluble fractions of corn oil phosphatides, according to the schedule of one capsule at a time three times daily to provide cumulative sequential dosages.

The treatment of humans having osteoarthritis by oral administration of the above-described dosage unit form of a composition containing as the active ingredient about 0.3 gram of the acetone-insoluble fractions of corn or maize phosphatides prepared according to Example I has been clinically studied. These studies have established the efficacy of the above compositions and the method of employing them in treating humans so afflicted. An improvement in the condition of the patient is usually observed within two to three weeks from the date the treatment is commenced. Objective signs may then be noted which demonstrate the effectiveness of the treatment. The pain experienced by the patient is alleviated. An obvious increase of motion is noted, as at the shoulder joints. The most common result obtained is a demonstrable flexibility of the finger joints which permits a patient to resume fine movements; such as, for example, piano playing, typewriting and knitting. Other results obtained which have been heretofore difficult, if not impossible to accomplish, are an increase in the mobility of the spine; improved posture and carriage; and speed and freedom of movement in walking. The specificity of this treatment is evidenced by a recurrence of the symptoms in almost every instance when the treatment is discontinued. A relapse usually occurs within about two weeks; and, in some instances, within several months. In isolated cases there were no recurrences after periods of three and seven years. It has been observed that with the resumption of the treatment, the symptoms in the patient are eliminated within about two or three weeks after the treatment is resumed.

That the results obtained in the use of this therapy represent a specific therapeutic effect of corn phosphatides, is evidenced by a number of observed facts. Particularly impressive, has been the fact that improvement in mobility of the affected joints has been objectively demonstrable in these patients and has paralleled subjective reports. Further evidence of specificity include a more or less uniform interval between start of treatment and evidence of improvement; high incidence of relapses when treatment is discontinued, with invariable improvement after its resumption; contrast between therapeutic effects of the phosphatides obtained from corn and soybeans respectively; and complete lack of effect in other forms of arthritis.

The observed effects in the use of this therapy have appeared with a rapidity and certainty never previously observed, with the possible exception of the rapid symptomatic improvement noted with cortisone and its derivatives or analogues. These latter preparations, however, provoke so many deleterious side effects, particularly in the aged, that their use is not recommended except by intraarticular injection. It is noteworthy, moreover, that

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prior to this invention no specific treatment, aside from the foregoing use of steroids, has been available, therapeutic efforts having been limited to the prevention of postural trauma by weight-reduction, correction of obvious deformities by orthopedic procedures, improvement of mobility of joints by physiotherapy, and relief of pain by analgesics, the most effective of which, phenylbutazone, is too toxic to permit of prolonged administration. On the basis of prior knowledge, therefore, the action of these corn phosphatides has been unexpected, and the use of this material appears to afford a physiological approach of great value to the solution of this problem, both from the standpoint of treatment and as a promising avenue toward an understanding of the fundamental etiology of this disease. While the corn phosphatides are known compounds and can be prepared by known methods, their therapeutic potentialities have never before been investigated.

It is to be emphasized that the dosage and dosage forms outlined herein are intended to be illustrative only and not restrictive. The amounts used have been chosen on the basis of clinical experience and are probably minimal. Larger doses may be administered and still larger doses may be used, if desired, since they are not harmful. It is contemplated that these formulations may be varied or modified to a considerable extent without departing from the spirit of this invention; such as, for example, by employing of other methods of extraction, purification, or preservation; or by using of excipients, diluents, or flavorings in the compositions; or by including these corn phosphatide fractions in mixtures with vitamin, nutritional, or therapeutic agents; or by alteration of dosage form; such as, liquid tonics, elixirs, and like preparations for oral use; or by admixing the corn phosphatide fractions with dietary items in therapeutically significant quantities. As outlined herein, the details of extraction, purification, preservation, and administration are intended to be illustrative, not restrictive; and it is not intended, therefore, to limit this invention to the specific embodiments herein set forth.

I claim:

1. A method of mitigating the symptoms of osteoarthritis in humans which comprises orally administering to a human having osteoarthritis doses of at least about 0.3 gram of the acetone-insoluble fractions of the phosphatides of a grain selected from the group consisting of corn and maize during the period in which said symptoms are exhibited by the human under treatment.

2. The method of claim 1 wherein the total daily dosage of said acetone-insoluble fractions is approximately 1.0 percent by weight based on the weight of the total daily fat intake of the human under treatment.

3. The method of claim 1 wherein the total daily dosage of said acetone-insoluble fractions is at least about 1.0 gram.

4. A method of mitigating the symptoms of osteoarthritis in humans which consists of administering orally to a human having osteoarthritis cumulative sequential doses of at least about 0.3 gram of the acetone-insoluble fractions of the phosphatides of a grain selected from the group consisting of corn and maize, and maintaining said treatment until the symptoms of osteoarthritis in the human under treatment are relieved.

5. A method of mitigating the symptoms of osteoarthritis in humans which comprises orally administering to a human having osteoarthritis sequential doses of from about 0.3 to about 1.0 gram of the acetone-insoluble fraction of the phosphatides of a grain selected from the group consisting of corn and maize during the period in which said symptoms are manifested.

6. The method of claim 5 wherein the total daily dosage provided by said sequential doses of said acetone-insoluble fractions is approximately 1.0 percent by weight based on the weight of the total daily fat intake

of the human to whom said sequential doses are orally administered.

7. An oral therapeutic composition in dosage unit form for mitigating the symptoms of osteoarthritis in humans having the disease comprising from about 0.3 to about 1.0 gram of the acetone-insoluble fraction of the phosphatides of a grain selected from the group consist-

ing of corn and maize per dosage unit and a pharmaceutical carrier.

References Cited in the file of this patent

UNITED STATES PATENTS

2,150,732 Thurman ----- Mar. 14, 1939