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FACILITATING HEALING OF BODY SURFACE WOUNDS BY INTRAVENOUS ADMINISTRATION OF N-ACETYL GLUCOSAMINE, GLUCOSAMINE, OR PHARMACEUTICALLY ACCEPTABLE ACID SALTS OF GLUCOSAMINE

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This invention relates to a new and useful process of promoting healing in the human body. More particularly, it relates to a new process of promoting healing in the human which comprises administering glucosamine and/or glucosamine derivatives to a person with a wound of the body surface. It also relates to compositions useful therefor. This application is a continuation-in-part of our copending application Serial No. 795,617, filed on February 26, 1959, now abandoned.

The healing of wounds of the body surface whether caused by trauma or surgery often times presents considerable difficulty, as described in numerous articles appearing in the medical literature. Many persons exhibit a slow rate of healing during which time considerable care must be taken to avoid the possibility of infection. Even with persons of normal healing rate, protection against infection must be provided, necessitating exacting care by medical personnel. The present invention provides a new and effective process of facilitating the healing of wounds of the body surface which materially reduces the time during which the possibility of infection is greatest as well as the time periods of close medical care and supervision. Other beneficial results of the present process are obvious from the following disclosure.

As previously mentioned, the process of the present invention comprises administering an effective amount of glucosamine and/or glucosamine derivatives to a subject with a wound of the body surface. While beneficial results will be noted with even lesser amounts, it is usually desirable to administer the glucosamine compound at a dosage of at least from about 10 to about 20 grams per day for best results. Often times it is found advantageous to administer the glucosamine compound at dosages as high as 200 grams per day and even higher.

The physician will indicate daily dosage of the instant therapeutic agents. The dosage and the route of administration will depend upon the extent of the wound and the healing rate of the individual patient. At times, the present therapeutic agents may be administered orally or locally, i.e. into the wound, and, at other times, parenterally, that is intravenously. Of course, these routes of administration may be employed concurrently to maintain an effective level of glucosamine compound in the subject patient. For example, the glucosamine compound may be administered to a patient orally at a dosage of from 10 to 20 grams per day for a period of four to five days before surgery, followed by intravenous administration at a dosage of between 100 to 200 grams in parenteral fluids, usually isotonic slaine, for four to five days postoperatively and then oral administration, as needed, of from 10 to 20 grams per day, usually for an additional four to five days.

The present invention contemplates the use of glucosamine, and/or glucosamine derivatives, such as lower N-alkanoylglucosamine, e.g. N-acetylglucosamine, phosphorylatedglucosamines, such as N-acetylglucosamine-6-phosphate, and glucosamine-6-phosphate, salt of glucosamine with pharmaceutically-acceptable acids, such as

hydrochloric, phosphoric, citric, gluconic, acetic, malic and the like. A particularly effective, and, for this reason, preferred glucosamine derivative is N-acetylglucosamine. The therapeutic agent is conveniently administered in the form of a suspension or solution, although it may also be administered as tablets or capsules. For oral use, suspensions or solutions of the therapeutic agent in pharmaceuticaly acceptable liquid media are particularly effective. Such liquid media are well known in the art, for example, water, aqueous glycols, sugar solutions and the like which may contain conventional flavoring and coloring agents. Tablets and capsules may be prepared from mixtures of the present compounds with well known pharmaceutical excipients such as starch, sugar, tapioca, certain forms of clay, and the like. For intravenous use, the present compounds are administered in isotonic solutions, such as isotonic saline.

For intravenous use, the present invention provides sterile aqueous compositions for intravenous administration which are prepared by dissolving the selected agent in an isotonic (about 0.1%) saline solution. It is preferred to employ the glucosamine compound at a concentration ranging from about 2% to about 20%, and preferably from about 3% to about 10%. Of course, lower concentrations provide some beneficial results but necessitate the use of extremely large volumes of intravenous solution which is usually not desirable. Higher concentrations, although operable, provide no appreciable advantage and thus are not recommended. The present invention also provides sterile solid compositions of glucosamine and/or glucosamine derivative together with salt for reconstitution with water to provide the above-described intravenous compositions. Of course, such solid compositions should contain a sufficient amount of salt to provide an isotonic saline solution when dissolved in water, that is, an isotonic amount of salt. The solid compositions preferably contain salt and glucosamine compound in a weight ratio ranging from about 1:20 to about 1:200. For example, when one gram of sodium chloride and 50 grams of N-acetylglucosamine are dissolved in one liter of water, a 5% glucosamine isotonic saline solution is obtained. Other such isotonic solutions of the glucosamine compound are prepared by reconstitution of the present solid compositions.

As a result of the administration of a glucosamine compound as herein described, in addition to a remarkable improvement in healing time, patients generally show a sense of well being, maintain body weight and, in some instances, unexpected weight gains are obtained. Further, such patients exhibit positive nitrogen balance in place of the usually expected negative balance during immediate postoperative period. Additionally, there is noted a lowering of blood cholesterol.

The following exemplifies the efficacy of the present new invention in promoting wound-healing. A female patient of 19 years of age and average weight with a mid-thigh amputation of a lower extremity suffered serious postoperative complications and poor wound healing. Daily intravenous administration of N-acetylglucosamine in isotonic saline (100 g. dissolved in 3 liters per day) to this patient for 4 days followed by daily oral administration of 20 grams of N-acetylglucosamine for 5 days resulted in a marked improvement in general condition with rapid healing of the wound.

A male patient of 28 years of age and average weight with postoperative septicemia and shock due to *E. coli* was being treated by hypothermia and with an artificial kidney for about three weeks. During this time his abdominal wound, i.e. the original operative incision, remained opened and gaping. At this time, the patient was treated with N-acetylglucosamine intravenously for

4 days, daily dosage being 100 grams in 3 liters of isotonic saline, followed by oral administration of 20 grams of N-acetylglucosamine daily for 5 days, which resulted in excellent, rapid healing of the wound. Similar results are obtained with glucosamine and other glucosamine derivatives as hereinbefore described with human as well as animal subjects.

Similar results were obtained when the present process was used in the treatment of other surgical patients. The results are summarized in the following table:

[NAG=N-acetylglucosamine]

Patient	Diagnosis and operation	Pre-operative treatment	Post-operative treatment	Serum transaminase units	Blood cholesterol, mgm./100 cc.	Urine N_2, gm.
I. 49 WF	Ulcerative colitis, Rx for several weeks with 300 mgm. cortisone daily. No complications. Discharged 11th P.O. day.	NAG, 10 gm. daily for 4 days.	1st P.O. day, NAG, 100 gms. I.V.; 2d P.O. day, NAG, 200 gms. I.V.; 3d P.O. day, NAG, 250 gms. I.V.; 4th P.O. day, NAG, 200 gms. I.V.	Pre-op. 21 1st P.O. 46 4th P.O. 23 10th P.O. 11	181 163 144 145	2.4 .500 .145
II. 63 CF	Perforated peptic ulcer, 3 days duration. No complications. Discharged 12th P.O. day.	None	NAG, 200 gm. I.V. daily for 5 days.	Pre-op. 28 1st P.O. 47 4th P.O. 26 10th P.O. 12	185 160 173 170	.500 .720 .300 .100
III. 63 CM	Subtotal gastrectomy chronic duodenal ulcer. Discharged 8th P.O. day. No complications.	NAG, 10 gm. daily for 4 days.	NAG, 200 gm. I.V. daily for 3 days.	Pre-op. 19 1st P.O. 41 4th P.O. 19 8th P.O. 4	204 210 180 170	.100 .100 Balance Balance
IV. 39 CF	Acute+chronic cholecystitis cholecystectomy. No complications. Discharged 10th P.O. day.	None	NAG, 200 gm. I.V. daily for 3 days.	Pre-op. 24 1st P.O. 31 4th P.O. 20 10th P.O. 8	142 160 160 130	.400 .400 .100 Balance

As it is obvious to those skilled in the art other therapeutically effective agents may be co-administered with the present agents, for example, compounds which serve as a source of high-energy phosphorus. Exemplary of this type of compound are phosphoenolpruvic acid and adenosine phosphates, e.g. mono and di-phosphates, which aid in the phosphorylation of intermediates in the metabolism of carbohydrate. Other such therapeutic agents may similarly be employed, e.g. broad spectrum antibiotics such as tetracycline, oxytetracycline ascorbic acid; tyrosine; etc.

The following examples are given by way of illustration and are not to be construed as limitations of the present invention, many variations of which are possible without departing from the spirit or scope thereof.

Example I

A mixture of 100 g. of N-acetylglucosamine and 1 g. of sodium chloride is thoroughly blended in a twin shell blender in an ethylene oxide-carbon dioxide atmosphere. The mixture is stored in an infusion bottle for reconstitution with one liter of sterile water for intravenous administration.

Other such mixtures are prepared in the same manner to provide solid compositions containing the following weight proportions of salt to glucose compound:

1 part salt to 50 parts glucosamine.
1 part salt to 100 parts glucosamine hydrochloride.
1 part salt to 200 parts glucosamine phosphate.
1 part salt to 20 parts N-acetylglucosamine.

Example II

Two thousand grams of N-acetylglucosamine is added to 20 liters of 0.1% aqueous saline solution. The resulting solution is filtered through a Seitz filter and stored in infusion bottles each containing one liter of 10% solution. The solution is useful for intravenous administration to human hosts with a wound of the body surface.

Example III

The procedure of Example II is repeated to prepare the following solutions:

20% glucosamine in 0.1% saline.
3% N-acetylglucosamine in 0.1% saline.
2% glucosamine hydrochloride in 0.1% saline.
20% N-acetylglucosamine in 0.1% saline.
5% glucosamine phosphate in 0.1% saline.
5% glucosamine citrate in 0.1% saline.
10% glucosamine gluconate in 0.1% saline.
3% glucosamine acetate in 0.1% saline.

What is claimed is:

1. A process for facilitating healing of a wound of the body surface which comprises administering intravenously from about 100 to about 200 grams of a compound selected from the group consisting of N-acetyl glucosamine, glucosamine and pharmaceutically acceptable acid salts of glucosamine.

2. A process for facilitating healing of a body wound of the body surface which comprises administering intravenously an effective amount of N-acetyl glucosamine.

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