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METHOD OF ADMINISTERING STREPTOKINASE SYSTEMICALLY

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This invention relates to chemotherapy and aims to provide a new method of administering streptokinase systemically.

It is frequently desirable in the treatment of a physical injury or disorder such as local infection or thrombosis, or such as may be caused by trauma, for instance, to enhance fibrinolysis at the site of the injury. Streptokinase is an excellent agent for use in the accomplishment of this. The evidence at hand indicates that it can react stoichiometrically with plasminogen to form a streptokinase-plasminogen complex that is a plasminogen activator. Evidently this activator adsorbs upon fibrin plasminogen at the site of an injury to create plasmin which appears to produce a lysis of the fibrin.

Prior to my invention, streptokinase was introduced into the system by intravenous or intramuscular injection. Each of those modes of administration is subject, however, to serious disadvantages and limitations. Attendance by, or a visit to a physician is necessary and patient acceptance is very poor. Pain and tenderness are experienced at the site of injection and administration by either of these routes may be accompanied by such undesirable side effects as elevation of temperature, nodule formation and allergic reactions. The side effects attending intravenous administration are apt to be particularly serious and may include shock, chills and high fever. Evidently the side effects that accompany the administration of streptokinase by injection result from the fact that, when a sufficient quantity is administered by this route to be effective at the site of an injury, there is also produced an undesirably high level in the blood.

I have discovered that it is possible to administer a safe but effective quantity of streptokinase in a manner that eliminates the pain of injection and at such rate that undesirable side effects are also avoided. This is accomplished in the practice of my invention by incorporating a dosage quantity of streptokinase in a dry medicament containing a compatible, pharmaceutically acceptable, water-soluble carrier for the streptokinase and then maintaining such medicament in contact with mucous membrane until dissolution of the medicament is effected. Thus, a dosage quantity of streptokinase can be incorporated in a tablet that is easily placed in the buccal cavity where it is retained until after dissolution of the tablet has taken place. During this period the streptokinase in the tablet evidently combines with plasminogen to form a streptokinase-plasminogen complex. Plasminogen is a component of saliva and mucous membrane itself is also a rich source thereof. The streptokinase-plasminogen complex then appears to penetrate the mucous membrane, for buccal administration thereof to a patient under treatment is followed by impressive anti-inflammatory effects, enhanced serum antithrombin activity, and an increase in anti-streptococcal antibodies as demonstrated through the use of the gel-diffusion technique of Ouchterlony (Ark. Kemi. Min. Geol. 26, B, 1, 1949, 26 B (14): 1–9, 1949).

In view of the fact that streptokinase is an inert protein molecule of large size, it would not be expected that placement in contact with mucous membrane would result in penetration thereof at any useful rate. Nevertheless, the rate of penetration is such that streptokinase, when administered in this manner, is an effective chemotherapeutic agent.

There have been no complaints of irritation or soreness of the mucous membrane with which the medicament was

in contact during administration of streptokinase pursuant to my invention, nor were adverse side effects encountered, so streptokinase can now be used in long term therapy and self-administration thereof by a patient is also easily effected. The elimination of adverse side effects that is accomplished by administration through penetration of mucous membrane is surprising since the streptokinase so administered was obtained in the same way as that which provoked such side effects when administered by injections, namely, from cultures of beta hemolytic streptococci which also produce smaller amounts of streptodornase and, in addition thereto, highly toxic substances.

Evidently mucous membrane permits penetration of the streptokinase-plasminogen complex at a rate that is automatically controlled so that the quantity thereof is sufficient to accomplish the intended purpose but an excessive level in the blood at any one time is avoided. Furthermore, administration by this route seems to result also in the exclusion of the toxic substances usually present in streptokinase preparations and, therefore, streptokinase of extreme purity is not necessary.

The amount of streptokinase that can be incorporated in a medicament to provide a dosage quantity ranges from about 5,000 to about 150,000 units thereof, a unit of streptokinase being that amount thereof which activates sufficient plasmin to bring about dissolution of a standard fibrin clot in ten minutes at 35° C. While a medicament containing about 5,000 units of streptokinase can be used with benefit and 150,000 units of streptokinase can be safely administered in a single dose, the quantity that I prefer to administer as a single dose in the practice of my invention ranges from about 10,000 to about 20,000 units of streptokinase. For instance, tablets containing 10,000 units of streptokinase, when administered buccally four times daily, provide a very effective regimen for the reduction of inflammation and swelling and the relief of pain associated with trauma and localized infections. Excellent results have been obtained through the buccal administration of tablets containing dosage quantities within the range of about 10,000 to about 20,000 units of streptokinase to patients afflicted with such disorders as abscess, thrombophlebitis, cellulitis, hematoma, leg ulcer, retinal-vein thrombosis, bronchiectasis, chronic bronchitis, acne vulgaris and migratory phlebitis.

In order that streptokinase may be administered in accordance with my invention, a dosage quantity thereof is combined with a dry carrier. Such a carrier may take the form of a water-soluble gelatin capsule. However, I prefer to incorporate the selected dosage quantity of streptokinase in a dry water-soluble tablet. Ordinary tableting procedure can be followed, using non-toxic excipients such as starch, soluble starch, lactose, magnesium oxide, magnesium carbonate, magnesium hydroxide, aluminum hydroxide, galactose, dextrin and dextrose.

I have found that the incorporation of a water-soluble stabilizing and solubilizing agent in tablets formulated pursuant to my invention augments the stability of the composition and causes it to dissolve readily. Such water-soluble stabilizing and solubilizing agent can be included with the excipients that are used, and as a part of the carrier for the streptokinase, or it can be utilized alone with the streptokinase. The water-soluble stabilizing and solubilizing agent that I now prefer to use is a solid polyethylene glycol having a molecular weight within the range of about 1,500 to about 4,000. Such a material is now marketed under the name "Carbowax." The amount of Carbowax used in a tablet may be from about 50 mg. to about 250 mg. Other water-soluble stabilizing and solubilizing agents that may be employed are a gum, such as karaya, tragacanth, agar, gum arabic, Indian gum, cherry gum and plum gum; a carbohydrate and derivatives thereof such as sorbitol, sorbitol laurate, sorbose, sorbitan,

mannitol, mannitol laurate, mannitan, dulcitol, dextrose, soluble starch, dextrin, levulose, inositol, arabinose and beta lactose; and methyl cellulose, gelatin and sodium chloride.

The streptokinase-containing tablets formulated in accordance with my invention also include, by preference, a salivant such as saccharin, i.e. benzo sulfimide $C_6H_4COSO_2NH$, and "Sucaryl," i.e. sodium, potassium and calcium salts of cyclo hexyl sulfamic acid, $C_6H_{11}NHSO_3H$, present in an amount from about $\frac{1}{128}$ to $\frac{1}{32}$ grain, suitably $\frac{1}{64}$ grain, per dosage unit. Such materials promote dissolution of the tablet upon buccal administration thereof.

Other substances that may be included in a medicament formulated according to my invention are insulin and an antibiotic such as penicillin, streptomycin, aureomycin, chloromycetin and terramycin.

In order that my invention will be fully available to those skilled in the art, specific preparations illustrating the practice thereof are described briefly:

Example I

15,000 units of streptokinase and 100 mgm. "Carbowax" 4000 are thoroughly admixed and the admixture thus produced is tableted.

Example II

15,000 units of streptokinase and 100 mgm. beta lactose are thoroughly admixed and the admixture thus produced is tableted.

Example III

15,000 units of streptokinase, 100 mgm. "Carbowax" 4000 and ¼ grain of saccharin are thoroughly admixed and the admixture thus produced is tableted.

Example IV

15,000 units of streptokinase, 100 mgm. "Carbowax" 4000, 100 mgm. lactose and ¼ grain of saccharin are thoroughly admixed and the admixture thus produced is tableted.

Example V

15,000 units of streptokinase, 100 mgm. beta lactose and $\frac{1}{32}$ grain of saccharin are thoroughly admixed and the admixture thus produced is tableted.

Example VI

15,000 units of streptokinase, 100 mgm. beta lactose and $\frac{1}{64}$ grain of "Sucaryl" are thoroughly admixed and the mixture thus produced is tableted.

This application is a continuation-in-part of my pending applications, Serial No. 485,593, filed February 1, 1955, and Serial No. 617,691, filed October 23, 1956, both now abandoned, which, in turn, were continuations-in-part of my copending application, now abandoned, Serial No. 463,328, filed October 19, 1954.

What I claim is:

1. The method of treating a body injury which comprises increasing fibrinolysis at the site of the injury through the systemic administration of streptokinase by placing a dosage quantity of streptokinase in contact with mucous membrane containing plasminogen, so that the streptokinase combines with plasminogen and permeates the mucous membrane.

2. The method of administering streptokinase systemically which comprises placing a medicament containing a dosage quantity of streptokinase and a compatible pharmaceutically acceptable water-soluble carrier therefor in contact with mucous membrane, and maintaining such contact until dissolution of said medicament is effected.

3. A method for the administration of a composition containing streptokinase as the essential active constituent which consists in placement and retention thereof buccally.

References Cited in the file of this patent

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