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(54) Titre : COMPOSITIONS PHARMACEUTIQUES SERVANT A GUERIR DES BLESSURES ET SE PRESENTANT SOUS LA FORME D'UNE POUDRE STERILE A BASE D'ACIDES AMINES ET DE HYALURONATE DE SODIUM

(54) Title: WOUND-HEALING PHARMACEUTICAL COMPOSITIONS IN THE FORM OF A STERILE POWDER BASED ON AMINO ACIDS AND SODIUM HYALURONATE

(57) Abrégé/Abstract:
This invention relates to wound-healing pharmaceutical compositions in the form of a sterile powder based on amino acids and sodium hyaluronate.

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(54) Title: WOUND-HEALING PHARMACEUTICAL COMPOSITIONS IN THE FORM OF A STERILE POWDER BASED ON AMINO ACIDS AND SODIUM HYALURONATE

(57) Abstract: This invention relates to wound-healing pharmaceutical compositions in the form of a sterile powder based on amino acids and sodium hyaluronate.

WOUND-HEALING PHARMACEUTICAL COMPOSITIONS IN THE FORM OF A STERILE POWDER BASED ON AMINO ACIDS AND SODIUM HYALURONATE

FIELD OF INVENTION

The present invention relates to wound-healing pharmaceutical compositions in the form of a sterile powder based on amino acids and sodium hyaluronate.

PRIOR ART

In the absence of suitable preventive actions, patients who are paralysed or bedridden for long periods are liable to ischaemic necrosis and ulceration of the tissues covering projecting bones, especially in the sacral, ischial, malleolar, heel and great trochanter regions.

Bedsores and chronic ulcerous wounds are usually treated with gentle massage to restore the circulation, possibly with mechanical removal of the necrotic tissue and cleansing with soap (which can cause oedema or dehydration), or with hydrophilic polymers, hydrogen peroxide or alcohol rubs (which can cause damage because the removal of the fats in the cutaneous tissue dries and cracks the skin).

Serious burns also require debridement of the affected area and removal of necrotic tissue.

DESCRIPTION OF THE INVENTION

It has now been found that the combination of some amino acids with sodium hyaluronate is particularly effective in promoting the process of cell reintegration which forms the basis for fast wound-healing, aiding the reconstruction of connective tissue and the consequent regeneration of epithelial cells.

The invention therefore relates to wound-healing pharmaceutical compositions in the form of a sterile powder, containing, as active ingredient, a combination of:

a) glycine and proline;

b) sodium hyaluronate; and possibly

c) lysine and leucine.

More particularly, the compositions according to the invention contain glycine, L-proline and sodium hyaluronate, and possibly L-lysine in hydrochloride form, and L-leucine.

The compositions according to the invention have proved a surprising adjuvant effect in promoting the healing of wounds which cannot be stitched and have seriously damaged the dermis, including with loss of skin substance, such as chronic ulcerous wounds, serious burns and bedsores. The compositions according to the invention can also be used for the treatment of surgical wounds.

The compositions according to the invention promote the elimination of necrotic tissue, thus facilitating more rapid regeneration of the tissues, and maintain the ideal humidity conditions to aid re-epithelialisation of the skin lesions, at the same time preventing the spread of germs.

According to the invention, the powder compositions will take the form of two separate capsules, one containing only proline, and the other containing the remaining active ingredients.

Separation of proline from the other active ingredients in the powder form is necessary for reasons of stability, because under conditions of low humidity, the proline $-NH_2$ group reacts with the hydroxyl groups on the hyaluronate, giving rise to a Maillard reaction, which considerably darkens the powder due to degradation of the amino acids.

Powders from the two separate capsules will be applied to the affected area after removing any foreign material by thorough washing with a hydrogen peroxide solution or saline solution, and removing of any excess blood with sterile gauze.

The compositions according to the invention will contain the various active ingredients within the following percentage ranges by weight:

- glycine 0.5 to 2%;
- L-proline: 0.2 to 1.5%;
- sodium hyaluronate: 0.5 to 3%;

and possibly

- L-lysine hydrochloride: 0.05 to 1%;
- L-leucine: 0.05 to 0.3%.

According to a preferred aspect, the compositions according to the invention will contain the various active ingredients in the following percentages by weight:

- glycine 1%;
- L-proline: 0.75%;
- sodium hyaluronate: 1.33%;

and possibly

- L-lysine hydrochloride: 0.1%;
- L-leucine: 0.15%.

The compositions according to the invention can be formulated suitably for the topical administration in the form of a sterile powder, and prepared according to conventional methods well known in pharmaceutical technology, such as those described in Remington's Pharmaceutical Handbook, Mack Publishing Co., N.Y., USA, using excipients, solubilisers, emollients, stabilisers, emulsifiers, pH regulators, and preservatives acceptable for their final use.

PHARMACOLOGICAL TRIAL

The ability of the compositions of the invention to heal chronic sores in elderly patients, diabetics and patients with vascular disease was evaluated.

In particular, 40 elderly patients suffering from bedsores, 36 Type II diabetics with ulcers extending to the lower limbs, and 32 patients with post-phlebitic ulcers were evaluated.

The treatment was given three/four times a week, depending on the severity of the lesions, by spreading the sterile powder on the wound.

The bedsores had to have a de-epithelialised area of over 10 cm^2 which had already been treated by conventional means for over 4 months, without any evident results. The type of bandage was irrelevant.

The sore was clinically evaluated and photographed before treatment in the fourth and eighth weeks of the trial. "Healing" was defined as closing of the wounds, and "improvement" as a reduction in size of the treated area exceeding 70% of the initial area.

By the fourth week of treatment 18 patients showed an improvement, namely a reduction in size of the sore of over 70%, and 2 were completely healed; by the end of the observation period (8th week), 24 patients were healed, 10 had improved and 3 patients presented a reduction of under 50% in the de-epithelialised area. 2 Patients were hospitalized for concomitant pathologies and 1 worsened due to superinfection.

Of the 36 diabetics with ulcers of various areas and depths, which had already been treated unsuccessfully for at least four months prior to our study, 12 were healed after four weeks' treatment, and another 30 no longer presented ulcerated areas by the end of treatment period. In 4 particularly serious cases there was an improvement, but the sore was still present by the end of the 8th week of treatment.

In patients with post-phlebitic ulcers who had already undergone conventional treatment for at least two months with no result, the administration of the sterile powder compositions according to the invention led to healing within one month in 18 patients and by the end of treatment (8th week) in another 10 patients, making a total of 28 out of 32 treated.

In conclusion, in the case of bedsores, diabetic and post-phlebitic skin ulcers, the sterile powder compositions according to the invention obtained healing indexes (expressed as % improvement) exceeding 80% by comparison with conventional treatment.

An example of a sterile powder formulation according to the invention is set out below.

EXAMPLE

Each box contains five blister packs, each containing two hard gelatin capsules (capsule A and capsule B).

Each capsule contains 438 mg (capsule A) and 150 mg (capsule B) of sterile powder.

Before topical application, one capsule A and one capsule B are opened, and the powder contained in them is poured onto the wound.

The compositions of capsule A and capsule B are as follows:

- ***Capsule A***

Each Capsule A (format 000 - Snap-Fit™ - Code: 23000), transparent bright pink, contains 438 mg of powder with the following composition:

Ingredients	**One capsule contains (mg)**
Powder	
Sodium hyaluronate	199.47
Glycine	182.10
L-Lysine hydrochloride	34.89
L-Leucine	21.54
Total	438.00

- ***Capsule B***

Each Capsule B (format 000 - Snap-Fit™ - Code: 43000), transparent, contains 150 mg of powder with the following composition:

Ingredients	**One capsule contains (mg)**
Powder	
L-Proline	150.0
Total	150.0

CLAIMS

1. A topical pharmaceutical composition in sterile powder form, containing as active ingredient a combination of:

a) glycine and L-proline; and

b) sodium hyaluronate;

wherein glycine, L-proline and sodium hyaluronate are comprised within the following percentage ranges by weight:

- glycine 0.5 to 2%;
- L-proline: 0.2 to 1.5%; and
- sodium hyaluronate: 0.5 to 3%.

2. The topical pharmaceutical composition of claim 1, the composition further comprising as active ingredient:

c) lysine hydrochloride and leucine.

3. The topical pharmaceutical composition of claim 2, wherein lysine hydrochloride is L-lysine hydrochloride, leucine is L-leucine and wherein L-lysine hydrochloride and L-leucine are comprised within the following percentage ranges by weight:

- L-lysine hydrochloride: 0.05 to 1%; and
- L-leucine: 0.05 to 0.3%.

4. The topical pharmaceutical composition of claim 1, wherein proline is L-proline, and wherein glycine, L-proline and sodium hyaluronate have the following percentage by weight:

- glycine 1%;
- L-proline: 0.75%; and
- sodium hyaluronate: 1.33%.

5. The topical pharmaceutical composition of claim 2, wherein lysine hydrochloride is L-lysine hydrochloride, leucine is L-leucine and wherein L-lysine hydrochloride and L-leucine have the following percentage by weight:

- L-lysine hydrochloride: 0.1%; and
- L-leucine: 0.15%.

6. Use of the topical pharmaceutical composition of claim 1 for treating a wound in a biological tissue.

7. The use of claim 6, wherein the medicament further comprises as active ingredient lysine hydrochloride and leucine.

8. The use of claim 6, wherein the wound is a chronic ulcerous wound, a serious burn, a bedsore, or a surgical wound.