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Application of levalbuterol formulation in treatment of skin and mucous membrane traumatic ulcers

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Title: APPLICATION OF LEVALBUTEROL FORMULATION IN TREATMENT OF SKIN AND MUCOUS MEMBRANE TRAUMATIC ULCERS

Abstract: Provided in the present invention is an (R)-albuterol pharmaceutically acceptable salt or pharmaceutical formulation thereof, and the application thereof in the preparation of drugs for the treatment of diseases such as skin ulcers, lesions, purulence, or delayed healing caused by trauma, pressure sores, tumours, diabetes, or coinfection. The pharmaceutical formulation contains the levalbuterol pharmaceutically acceptable salt, or the levalbuterol pharmaceutically acceptable salt and hormones, antibiotics, or anti-inflammatory drugs.
Application of Levalbuterol Formulation in Treatment of Skin and Mucous Membrane Traumatic Ulcers

This Patent included R-albuterol and its related external formula on the application in skin damage, ulcer and delay wound healing caused by wound, burning, bedsore, tumor, diabetes, et al.

Background

RS-albuterol, an enantiomer which contained S-albuterol and R-albuterol, is a β receptor agonist with a chiral center. Base on related pharmacology study, the R-albuterol and RS-albuterol can relieve the airway hyperreactivity induced by the convulsion, which relax tracheal smooth muscle, while S-albuterol may increase the tracheal collapse, instead relax it. In a human bronchus in vitro study, S-albuterol may activity macrophage and further promoted the contracts caused by histamine and interleukin 4(LTC4), and increase the catalase generation in eosinocyte. Contrastively, R-albuterol presents anti-inflammation activity, inhibit the proliferation and secretion of IL-2 and interferon-γ under the stimulation of phytohemagglutinin. There is research report that R-albuterol cure lupus erythematosus, the discoid lupus erythematosus (DLE) and Subacute lupus erythematosus (SCLE) area significantly decrease after the R-albuterol treatment, compare with the placebo groups. And R-albuterol can also cure other connective tissue diseases. It may inhibit this abnormal autologous reaction by stimulating the T cell.

Lupus erythematosus and connective tissue disease are autoimmune diseases, usually associated with the hormonal antibody or T cell abnormal, which does not involve trauma and infection. However, the current literature does not report whether R-albuterol is effective in inhibiting skin tissue ulcers and/or combined bacterial infections caused by external trauma, burn, tumors, diabetes or infections.

Detail of Invention

Unlike lupus erythematosus and connective tissue diseases and other autoimmune diseases, external trauma, burns, tumors, diabetes or infections cause
skin tissue ulcers and (or combined) bacterial infections. Skin ulcers are the tissue damage and ulceration on skin or mucosal surface, which usually covered with pus, necrotic tissue or crusts, leave scar, caused by infected, trauma, nodules or tumor ulceration, differed from size, shape, depth and the development process, and associated with chronic infection. Chronic skin ulcers are common diseases, frequently disease, extended course and difficult to cure. The cause of the disease may be trauma, burns, scalds, bedsore, may also be combined with infection, eczema, diabetes and cancerous cancer, or the merger of the above factors.

This present invention has unexpected found that the use of external preparations for R-albuterol can be used to treat tissue trauma and / or combined bacterial infections and to promote the recovery of tissue ulcer wounds, thereby promoting wound healing. R-albuterol (sulphate) has the following structure:

![Chemical structure of R-albuterol](image)

This present invention contented R-albuterol or the pharmaceutically acceptable salt associated organic or inorganic acids, including sulfates or bisulfates, hydrochlorides, hydrobromides, dihydrogenphosphate, methanesulphonate, bromide, acetate, oxalate, maleate, fumarate, succinate, 2-naphthyl sulfate, gluconate, citrate, tartrate, lactate, pyruvate, isethionate, benzene sulfonate, and p-toluene sulfate, etc.

Additionally, R-albuterol can be prepared as topical ointment, spray, patch, powder, granules and other external formulations or body cavity suppositories, ointment, as well as in the skin table muscle injection or various sustained-release agent.

The present invention also includes a novel combination use with hormonal drugs. In the present invention, R-albuterol and its pharmaceutical acceptable salt, used in combination with various types of corticosteroids in different proportions of
combinations, can be made of various types of preparations, topical for the treatment of skin tissue ulcers due to trauma, burns, scalds, tumors, eczema, diabetes or infection (or combined) bacterial infections, as well as the promotion of the above causes of trauma caused by wound healing. Combination of those together play an important role in the effect of synergy treatment. The above corticosteroids include budesonide, ciclesonide, beclomethasone dipropionate, mometasone furoate, Naloxone, fluticasone propionate, triamcinolone acetonide, fluticasone, and their physiologically acceptable salts or solvents.

The present invention also includes a novel combination with anti-inflammatory and immunomodulator drugs. The amount of treatment with R-albuterol and its pharmaceutically acceptable salts with anti-inflammatory or immunomodulators such as interleukin receptor antagonists, leukocyte irritation, tumor necrosis factor (TNF) antibody, interferon and integrin, and so on.

The present invention also includes a novel combination with antibiotics such as ofloxacin or levoﬂoxacin, amoxicillin, erythromycin, other topical antibiotics and other skin trauma treatment of chemical drugs, biological drugs or botanicals, epidermal growth factor and other drugs.

The above combination therapy can be prepared into topical preparations such as creams, patches, sprays, powders, granules, bodies intrauterine suppositories or various sustained release agents. Topical or body cavity for use in the treatment of trauma, burns, burns, tumors, eczema, diabetes or infection caused by skin tissue ulcers and (or combined) bacterial infections, as well as to promote the above causes of trauma wound healing to play a synergistic or synergistic therapeutic effect.

The combination could be through a simultaneous, sustained, or separate mode of administration, thereby increasing the therapeutic index or serving the drug positive synergies. The dosage range of the anti-inflammatory agent could be adjusted according to the symptoms and age and the therapeutic target of the main drug.

The features and advantages of the invention are apparent from the following detailed description. It should be understood, however, that the detailed description, these specific embodiments and the embodiments of the present invention are used for
Because those skilled in the art will be easy to find various changes and modifications within the spirit and scope of the invention.

**Examples**

**Example 1:**
Preparation of R-albuterol Cream

R-albuterol cream preparation method is as follows: Preparation of hydrophobic phase: accurate weighing (by volume) 5% petrolatum, 10% of paraffin oil, 5% gelatin, 6% glycercyl monostearate, plus 0.5% tween 80 (26.5%), heated to 70 °C. Preparation of hydrophilic phase: accurate weighing (by volume) 0.5% R-albuterol sulfate, 5% propylene glycol, 0.5% benzyl alcohol, plus water to 73.5%. Heated to 70 °C. The two phases were mixed (100%) and the mixture was cooled with stirring, i.e., R-albuterol Ointment. The ratio of R-albuterol and excipients can also be adjusted as required, such as from 0.01% to 99% albuterol.

**Example 2:**
Experimental study on the effect of (R)-albuterol on skin trauma in mice

A total of 60 KM mice weighing 25-29 g were randomly assigned to four experimental groups of A, B, C and D, each group had 15 mice. And the acute trauma models were made in the skin of the hair removal area of the mice. Do full-thickness skin resection with a circular punch, resulting in a diameter of 8mm round hole (or two incisions, one in the back, one in the buttocks), single cage raising one mouse. A, B, C, D groups were smeared homemade (R)-albuterol ointment, blank excipients and positive control drugs (ofloxacin). Dosage: once a day (extended to 2~3mm, thickness of about 0.5mm).

The daily changes of wound morphology were observed, photography and measurement of wound diameter were done, the wound scab time and healing time were recorded. The standards of healing are wound closed, surface dry, eschar fall off
and return to normal. The healing time was recorded. The full-thickness skin of wound with the surrounding normal tissue was fixed by 10% formalin every five days, and prepared paraffin sections. The paraffin sections were stained with HE, and wound granulation tissue growth and re-epithelialization were observed under light microscopy.

Area calculation method: the wound area was measured by aseptic film or transparent sulfuric acid paper. The Image Pro software was used to calculate the wound area (plane measurement method). Percentage of wound healing: healing rate = original wound - present wound / original wound. The variance analysis of single-factor repeated measurement data was used to analyzed the wound area.

RESULTS: After eight days observation, it was found that the percentage of wound healing in mice was 85.7% in the (R)-albuterol group, 84.5% in the positive control group and 48.5% in the blank group. After the same period of time, the healing area of the mice in the administration group was significantly larger than that in the blank excipients mice. Attachment Figure is the comparative effect of (R)-albuterol on skin wound healing in mice (Fig. 1).

<table>
<thead>
<tr>
<th>Blank excipients</th>
<th>Control drugs (ofloxacin)</th>
<th>(R)-albuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Day 8</strong></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Fig. 1 Comparison of the effect of R-albuterol sulfate on wound healing in mice

Example 3:
Experimental study on the skin trauma of mice with (R)-albuterol and levofloxacin compound ointment.

Ten KM mice weighing 26-28g were randomly assigned to A and B experimental
groups, each group had 5 mice. And the acute trauma models were made in the skin of the hair removal area of the mice. Do full-thickness skin resection with a circular punch, resulting in a diameter of 8mm round hole, single cage raising one mouse. A and B groups were coated with homemade (R)-albuterol ointment and (R)-albuterol and levofloxacin compound ointment. Dosage: once a day (extended to 2 ~ 3mm, thickness of about 0.5mm).

The wound area (plane measurement method) and percentage of wound healing were observed and calculated according to the method described in Example 2.

**RESULTS:** After eight days observation, it was found that the percentage of wound healing in mice was 88% in the (R)-albuterol group, and 90% in the compound group. The healing area of the mice in the compound group was significantly larger than that in the (R)-albuterol group.

The descriptions above are the illustrative embodiments of the present invention, and have no formal limitation. Any simple modification or equivalent variation which is in accordance with the technical spirit of the present invention is equivalent embodiment of the present invention, it is within the scope of the technical solution of the present invention.
Claims

Listing of Claims

1. A method of treating a wound, trauma or ulcer in skin or a mucous membrane with delayed healing comprising administering R-albuterol or a pharmaceutically acceptable salt thereof to a patient in need thereof.

2. The method of claim 1, wherein the salts are sulfate or hydrosulfate, hydrochloride, hydrobromate, dihydric phosphate, metilsulfate, bromate, acetate, oxalate, maleate, fumarate, succinate, 2-naphthyl sulfate, gluconate, citrate, tartrate, lactate, pyruvate, hydroxyethyl sulfonate, benzene sulfonate and tosilate.

3. The method of claim 1, wherein the pharmaceutical compositions are R-albuterol salt in combination with corticosteroids. The corticosteroids include budesonide, ciclesonide, beclomethasone, mometasone furoate, flunisolide, fluticasone propionate, triamcinolone acetonide, fluticasone and their salts which can be used in physiology.

4. The method of claim 1, wherein the pharmaceutical compositions are R-albuterol salt in combination with anti-inflammatory or immunomodulatory agents. The anti-inflammatory or immunomodulatory agents include interleukin receptor antagonist, leukocyte stimulating factor, epidermal growth factor, tumor necrosis factor (TNF) antibody, interferons, and integrin.

5. The method of claim 1, wherein the pharmaceutical compositions are R-albuterol salt in combination with topical use antibiotics. The antibiotic include topical antibiotics including ofloxacin, levofloxacin, amoxicillin and erythromycin and other botanicals antibiotics.

6. The method of claim 1, wherein the pharmaceutical compositions are topical ointment, patch, liniment, spray, powder, granule, drops, suppositories in the body cavity and controlled/slow release agents.

7. The method of claim 1, wherein these wounds on skin or mucous membrane are present as localized lesion edema or ulcer that gorged with blood and/or covered in pus, and/or contains necrosis with pus or dead tissue on the surface of skin, mucous membrane or cornea and long lasting open wound.
8. The method of claim 1, wherein the wound, trauma or ulcer in skin or mucous membrane with delayed healing are the results of external trauma, burns, scalds, bedsores, or potential microbial infections, diabetes, eczema, carcinoma in-situ and/or combined conditions above.
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