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(54) Titre : PREPARATION POUR LE TRAITEMENT DE CHANGEMENTS VASCULAIRES  
(54) Title: PREPARATION FOR THE TREATMENT OF CIRCULATORY CHANGES

(57) **Abrégé/Abstract:**

The invention is relative to a preparation in a novel indication which reduces the formation of deposits of thrombocytes in the vascular system. This prevents the occurrence of constrictions in the vessels. The preparation is alpha-lipoic acid (thioctic acid), which can be administered in several forms of administration such as e.g. by injection or by tablet and which is largely free of side effects. Moreover, it can be shown in the case of smokers that the substance has a prophylactic effect in that the typical supersensitivity of the thrombocytes, which constitutes a cause for the appearance of premature vessel changes, is braked.



## ABSTRACT

The invention is relative to a preparation in a novel indication which reduces the formation of deposits of thrombocytes in the vascular system. This prevents the occurrence of constrictions in the vessels. The preparation is alpha-lipoic acid (thioctic acid), which can be administered in several forms of administration such as e.g. by injection or by tablet and which is largely free of side effects.

Moreover, it can be shown in the case of smokers that the substance has a prophylactic effect in that the typical supersensitivity of the thrombocytes, which constitutes a cause for the appearance of premature vessel changes, is braked.

$\alpha$ -lipoic acid (=thioctic acid) is chemically 1,2-dithiacyclopentane-3-valeric acid. The production of the free R-thioctic acid is described, e.g., in DE-OS 41 37 773.

The invention relates to R,S-thioctic acid in reduced or oxidized form, its isolated enantiomers (R-thioctic acid and S-thioctic acid) and metabolites in the form of the free acid as salts, esters or amides. Thioctic acid is a component of the cell metabolism and is therefore found in many plants and animal organisms. It acts as one of the coenzymes in the oxidative decarboxylation of pyruvate and other  $\alpha$ -keto acids. Thioctic acid has been used for some time in various diseases, among others, diseases of the liver, liver damage due to mushroom poisoning and in diabetic and alcoholic polyneuropathy, a change of peripheral nerves accompanying metabolic diseases.

The chemistry and biochemistry of  $\alpha$ -lipoic acid are discussed in the article by Schmidt, Grafen and Goedde, Ang. Chem. 77 (1965), pp. 900-911 and in Reed, Vitamins, Hormones 20 (1962), pp. 1-38.

The biosynthesis of derivatives of  $\alpha$ -lipoic acid is discussed by Gunsalus, Barton and Gruber in J. Amer. Chem. Soc. 78 (1956) pp. 1763-1766.

The present invention relates to a substance which offers good effects in a novel application for the treatment of circulatory changes, for example, changes in the blood flow and circulation, resulting in deposits on vessel walls.

Such circulatory changes are present in many diseases, a few of which are cited in the following by way of example:

- a) Smokers;
- b) Diabetics; and
- c) Lipometabolic disturbances.

Furthermore, the preparation in accordance with the invention is suitable for prophylactic use in the above-mentioned patients in order to prevent these changes from occurring at all, which can lead clinically to the development of high blood pressure.

Thus, in one aspect, the present invention provides a preparation for the prevention or treatment of circulatory changes comprising alpha-lipoic acid (R,S-thioctic acid) in reduced or oxidized form, its isolated enantiomers and metabolites in the form of the free acid, as salts, esters, or amides.

In another aspect, the invention provides a preparation for the prevention or treatment of circulatory changes which consisting essentially of alpha-lipoic acid (R,S-thioctic acid) in reduced or oxidized form, or its isolated enantiomers and metabolites in the form of the free acids, salts, esters, or amides.

The  $\alpha$ -lipoic acid may be present in the preparation in a minimum intravenous dosage amount of 50mg or in a minimum oral dosage amount of 20mg.

In one aspect, the invention provides a preparation wherein the  $\alpha$ -lipoic acid is to be used over a rather long time period, at least over 7 days, in order to bring about the desired effect.

In another aspect, the invention provides use of the preparation for the prevention, delay, or treatment of circulatory disturbances.

2a

## PHARMACOLOGICAL EXAMPLE 1

Male Wistar rats with an average initial weight of approximately 120g were used. The control animals received standardized rat food, 30 animals (10 per group) received 10g/animal/day of a special cardiovasopathogenic diet (see below for composition). Water was available for the animals ad libitum. One group (10 animals) was treated daily with 0.5 ml/100 g 0.9% NaCl solution i.p. The

animals of the two other groups (10 rats each) were treated daily with thiocetic acid (15 and 30 mg/kg) i.p. The blood pressure was measured non-invasively at weekly intervals with the aid of a suitable blood pressure instrument (sphygmomanometer).

Group	Rise in blood pressure after 7 weeks (mm Hg)
Control	3.5
Pathogenic diet	31.4
15 mg/kg	14
30 mg/kg	14.5

The test was carried out in accordance with the method of I. Szelenyi, J. Sos, and J. Rigo "Action of Magnesium Orotate and Orotic Acid on the Elevation of Blood Pressure Initiated in Animal Experiments and Cardiopathogenic Changes in the Heart Muscle" (Deutsches Medizinisches Journal, 21st year, vol. 22-Berlin, Nov. 20, 1970).

Many of the diseases cited above begin slowly and without clear symptoms. Problems with the legs frequently occur independently of the basic disease. The patients must often remain standing because they have severe pains. However, there are also changes in the heart which can result in angina pectoris up to infarct and changes in the brain which can cause temporary inadequate circulation in mild cases or can be expressed in the form of paralyses or other neurological symptoms in time.

The active mechanism of the appearance of vessel changes which adversely affect the circulation as a consequence takes place to an essential degree via the blood platelets, which are designated in medicine as thrombocytes. The blood platelets have a physiological function of repairing tissue damage in which they accumulate where collagen is present. This means for the vascular system that collagen is offered at locations where the inner layer is defective and healthy thrombocytes accumulate in order to make possible jacketing and regeneration. In the case of certain diseases and especially in the case of smokers the individual thrombocyte is supersensitive, that is, it reacts readily with extremely small amounts of collagen with accumulation on the vessel wall. This has the consequence that thrombocytes are superimposed on a practically healthy vessel wall, thus constricting the vessel. This results subsequently in an obligatory decrease in the flow.

The present invention is directed to a remedy in this connection. In this regard, the invention provides  $\alpha$ -lipoic acid (thioctic acid) as a substance which selectively inhibits the supersensitive thrombocytes as to thrombocyte function and normalizes their physiological functions. In comparison to other substances which also act on the thrombocyte function, hardly any side effects occur with  $\alpha$ -lipoic acid.

$\alpha$ -lipoic acid, also called thioctic acid, is commercially admitted in the form of tablets and of ampoules; the dosage in the case of tablets is approximately 200 mg and in the case of ampoules the dosage fluctuates on the order of 10 mg to 50 mg/ml. The main

areas of indication are diabetic polyneuropathy as well as, in some countries, certain diseases of the liver.

It turned out in the case of smokers that  $\alpha$ -lipoic acid, when prophylactically administered, eliminates to a large extent the effect of increasing the thrombocyte function typical for smokers. In addition, a distinctly better circulation of the skin was also found in numerous smokers with  $\alpha$ -lipoic acid.

In the case of patients with dysglycemia (diabetes mellitus) it turned out that in the early stage largely normal thrombocyte functions likewise occur for a rather long time, which appears to be unusual and speaks for an improved circulation.

Based on previous clinical experiences, there are indications that the subject of the invention inhibits the increase of circulatory disturbances and the development of high blood pressure and on the other hand, when administered prophylactically to diabetics, the appearance of these disturbances is significantly delayed.

The invention is explained in detail in the following in examples.

#### EXAMPLE 2

It turned out in the case of smokers with intravenous administration of 1 ampoule  $\alpha$ -lipoic acid over 7 days that the levels of thrombocyte function on collagen were inconspicuous but in a group of smokers of the same age without  $\alpha$ -lipoic acid distinctly higher values were registered. Additional measurements of circulation carried out on the skin of the legs showed distinctly higher values in the  $\alpha$ -lipoic acid group than without  $\alpha$ -lipoic acid,

which indicates an improvement of circulation in the microcirculation.

#### EXAMPLE 3

The values of the thrombocyte function were determined in a volunteer test subject (non-smoker), which were inconspicuous. After the smoking of 1 cigarette, distinctly higher values were found. The same experiment was repeated on the next day in which a dose of 400mg  $\alpha$ -lipoic acid had been taken previously in tablet form. There was no increase in the values.

#### EXAMPLE 4

$\alpha$ -lipoic acid was administered for 1 week to patients who had diabetes for several years. This group exhibited inconspicuous thrombocyte levels. On the other hand, a largely identical control group exhibited distinctly higher values.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A preparation for the prevention or treatment of circulatory changes comprising alpha-lipoic acid (R,S-thioctic acid) in reduced or oxidized form, or its isolated enantiomers and metabolites in the form of free acids, salts, esters, or amides, in admixture with a suitable pharmaceutically acceptable diluent or carrier.
2. A preparation for the prevention or treatment of circulatory changes consisting essentially of alpha-lipoic acid (R,S-thioctic acid) in reduced or oxidized form, or its isolated enantiomers and metabolites in the form of the free acids, salts, esters, or amides, in admixture with a suitable pharmaceutically acceptable diluent or carrier.
3. The preparation according to claim 1 or 2, wherein the alpha-lipoic acid (R,S-thioctic acid) is present in a minimum intravenous dosage amount of 50 mg.
4. The preparation according to claim 1 or 2, wherein the alpha-lipoic acid (R,S-thioctic acid) is present in a minimum oral dosage amount of 20 mg.
5. The preparation of claim 1 or 2, wherein the alpha-lipoic acid is present in a dosage amount of 15 mg/kg patient - 30 mg/kg patient.
6. The preparation according to any one of claims 1 to 5, wherein the alpha-lipoic acid is present in a dosage amount

suitable for administration over a period of at least 7 days.

7. Use of the preparation according to any one of claims 1 to 6, for the prevention or delay of circulatory disturbances.

8. Use of the preparation according to any one of claims 1 to 6, for the prevention or delay of circulatory disturbances in a smoker.

9. Use of the preparation according to any one of claims 1 to 6, for the manufacture of a medicament for blocking or reducing increased reactivity of thrombocytes in a type I, type II, or insulin resistant diabetic.

10. Use of the preparation according to any one of claims 1 to 6, for the prevention of the accumulation of thrombocytes on a blood vessel wall.

11. Use of the preparation according to any one of claims 1 to 6, for blocking or reducing increased reactivity of thrombocytes.

12. Use of the preparation according to any one of claims 1 to 6, for blocking or reducing increased reactivity of thrombocytes in a smoker.

13. Use of the preparation according to any one of claims 1 to 6, for blocking or reducing increased reactivity of thrombocytes in a type I, type II, or insulin resistant diabetic.

14. Use of the preparation according to any one of claims 1 to 6, for the manufacture of a medicament for the prevention or delay of circulatory disturbances.

15. Use of the preparation according to any one of claims 1 to 6, for the manufacture of a medicament for the prevention or delay of circulatory disturbances in a smoker.

16. Use of the preparation according to any one of claims 1 to 6, for the manufacture of a medicament for blocking or reducing increased reactivity of thrombocytes in a smoker.

17. Use of the preparation according to any one of claims 1 to 6, for the manufacture of a medicament for the prevention of the accumulation of thrombocytes on a blood vessel wall.

18. Use of the preparation according to any one of claims 1 to 6, for the manufacture of a medicament for blocking or reducing increased reactivity of thrombocytes.

19. Use of alpha-lipoic acid (R,S-thioctic acid) in reduced or oxidized form, or its isolated enantiomers and metabolites in the form of free acids, salts, esters or amides, to produce a preparation for preventing and slowing the progression of high blood pressure in smokers, diabetics, or patients with lipometabolic disturbance.

20. A commercial package containing as active pharmaceutical ingredient alpha-lipoic acid (R,S-thioctic

acid) in reduced or oxidized form, or its isolated enantiomers and metabolites in the form of free acids, salts, esters, or amides, together with instructions for its use for the prevention or treatment of circulatory disturbances.