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<[US 5,840,755](#)>

<[US 5,863,941](#)>

United States Patent 4,765,986

Liedtke, August 23, 1988

Medicinal plaster for systemic use

Abstract. A medicinal plaster for dermally applied medication which is attachable to the skin, which comprises first and second parts joined in a housing which is closed at the top side and open on the lower side thereof towards the skin surface, said first part at the lower side comprising a drug-containing carrier substance which melts at approximately physiological body temperature; and said second part at the top side, which is affixed to said first part, comprises a porous and flexible synthetic material having approximately the same diameter as said first part.

Claims

1. A medicinal plaster for dermally applied medication which is attachable to the skin, which comprises first and second parts joined in a housing which is closed at the top side and open on the lower side thereof towards the skin surface, wherein said first part at the lower side is a disc comprising a drug-containing carrier substance, said carrier substance being selected from the group consisting of gelatin; one or more triglycerides of unsaturated carbon acids having 10-18 carbon atoms; and a mixture of one or more of said triglycerides of saturated carbon acids having 10-18 carbon atoms and one or more mono- and diglycerides of saturated and unsaturated, or both, carbon acids having 8-12 carbon atoms; and a mixture of gelatin with one or more of said triglycerides; and a mixture of gelatin with a one or more of said triglycerides and one or more of said mono- and diglycerides; said carrier substance melting at approximately physiological body temperature so that the drug is released from the liquid phase of the carrier substance; and said second part is a disc consisting of a porous and flexible polyurethane-ether foam or polyurethane-ester foam having approximately the same diameter as said first part; said carrier substance disc being mechanically connected with the polyurethane foam disc by at least partial penetration of the carrier substance into the pores of the polyurethane foam disc.
2. The medicinal plaster according to claim 1, wherein said drug contained in said carrier is not exclusively homogeneously dissolved and is contained in said carrier substance in technical depot form.
3. The medicinal plaster according to claim 1, wherein the drug-containing carrier substance is distributed in the pores of the polyurethane foam disc.
4. The medicinal plaster according to claim 1, wherein the polyurethane foam disc has a mechanical barrier at the top side thereof.
5. The medicinal plaster according to claim 1, wherein the plaster is one-sided self-adhesive plastic foil on the lower side of which is a one-sided self-adhesive closed pore foam ring and, in the whole of the foam ring, the polyurethane foam disc with carrier substance is joined to the plastic foil.
6. The medicinal plaster according to claim 1, wherein the carrier contains one or more drugs for the treatment of high blood pressure or angina pectoris in an amount of 0.5-10% by weight based on the carrier substance.
7. The medicinal plaster according to claim 6, wherein said carrier contains 2-8% by weight of said drugs.
8. A method of dermally administering medication with enhanced skin absorption, which comprises attaching the medicinal plaster of claim 1 to mammalian skin, thereby effecting the administration of said medication.
9. The method according to claim 8, wherein said mammalian skin is human skin.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a medicinal plaster for improved skin absorption of dermally applied medication.

2. Description of the Background

It is known that systemic medicinal effects can be obtained with medicinal plasters or so-called therapeutic plaster systems, designated lately as transdermal therapeutic systems. At present, this type of system is used in connection with the drug scopolamine for kinetosis, nitroglycerine for coronary heart disease and clonidine for hypertension, as well as for transdermally administered estrogens. However, the plaster systems used to date are technically complex and the attainable absorption rates, measured through the systemic drug concentration in the blood, are clearly less than those after oral administration. In addition, the systems show considerable variation from patient to patient with regard to the determined serum concentrations of the administered drugs.

The plaster systems entail diffusion units in which the medications are released by diffusion at controlled rates from a mechanically fixed drug reservoir, usually tissue tolerant polymers. The systems used are currently divided into membrane systems, i.e., membrane plaster and matrix systems. In the membrane systems the drug, after release from the carrier substance, must permeate a membrane, which serves as a control element for the constant absorption rate. Thereby, it is possible to attain a release characteristic, which approximately corresponds to pharmacokinetics of zero order. In matrix systems, the drug stored in depot form diffuses directly from the polymer matrix into the skin.

The transfer of medication from the plaster system into the skin occurs according to the laws of diffusion, quantified in the diffusion principles according to Fick: $Q = D \cdot F \cdot (C_{sub.1} - C_{sub.2}) \cdot t / d$ whereby per time unit (t) the drug amount transported (Q), the diffusion rate, is dependent on the diffusion coefficient (D), the exchange surface (F) and the concentration difference ($C_{sub.1} - C_{sub.2}$) as well as the diffusion distance or the layer thickness (d). It is observed that plasters with mechanically rigid matrices do not optimally follow the diffusion conditions.

Thus, the polymer matrices and biological membranes such as irregularly formed complementary skin surface, which represent the exchange surface, adhere such that there is an incomplete utilization of the biologically available absorption surface. Simultaneously, the diffusion distance is thereby increased in several areas of the adhering absorption surface of the plaster. Both effects mean a deterioration of the general diffusion conditions. As, in addition, the speed of the diffusion process also depends on the temperature, the temperature exchange between the technical resorption area and the drug reservoir on the one hand, and the skin surface on the other hand, is not optimally attained with the incomplete superposition. Another disadvantageous effect is the relatively slow water absorption which is needed for the dissolving process of the medication.

In addition, the production of membrane and matrix systems is technically costly and requires special apparatus, which causes higher costs than for the production of oral forms of application.

Accordingly, a need clearly exists for a relatively simple and inexpensive means by which dermally applied medications can be applied with excellent skin absorption.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a relatively simple and inexpensive means by which dermally applied medications can be administered with excellent skin absorption.

According to the present invention, the foregoing and other objects are attained by providing a medicinal plaster for dermally applied medication which is attachable to the skin, which entails two joined parts in a housing which is closed at the top and open on the lower side towards the skin surface, said first part at the lower side being a drug-containing carrier substance which melts at physiological body temperature; and said second part at the top side, being affixed to said lower side carrier

substance, is a porous and flexible synthetic material having approximately the same diameter as said lower side disk.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the present medicinal plaster in a cross-sectional view.

FIG. 2 illustrates the present medicinal plaster in an exploded diagram.

FIG. 3 illustrates a partial enlargement of the present medicinal plaster in a cross-sectional view.

FIG. 4 illustrates a detailed modification of the present medicinal plaster in a cross-sectional view.

FIG. 5 illustrates a detailed modification of the present medicinal plaster in an exploded diagram.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

According to the present invention, the medication is contained in a solid carrier substance, preferably shaped as a disk, which melts at physiological body temperature, whereby the carrier substance is affixed, to the bottom side of a porous and flexible synthetic material of approximately the same diameter and the two joined parts are located in a housing, closed on top and open towards the skin side, which may be attached to the skin.

In a further aspect of the present invention, it is possible to utilize non-homogeneously dissolving drugs which are absorbed in the carrier substance in pharmaceutical technical depot form in order to provide for delayed drug release.

In another aspect of the present invention, two or more layers having varying melting behavior are applied on top of each other in order to attain a varying successive absorption rate.

In a further aspect of this invention, the carrier substance is distributed in the pores of the whole synthetic material in order to better retain the full flexibility of the synthetic material.

In another aspect of this invention, the synthetic material is provided on its top side with a mechanical barrier layer in order to obtain a better mechanical separation between carrier substance and housing.

In still a further aspect of this invention, the synthetic material is preferably made of polyurethane foam of the ether type or of the ester type in order to attain particularly favorable physical properties together with a physiological indifference or tolerance.

In another aspect of the present invention, carrier substances of solid fats/adepts solidus or mixtures of various solid fats are preferably introduced into the pores of a synthetic material of polyurethane foam of the ether type or ester type, in order to obtain particularly favorable physical and biopharmaceutical properties together with a good physiological tolerance.

According to the present invention, carrier substances of gelatin or mixtures of gelatin and solid fats are preferably introduced into the pores of a synthetic material or polyurethane foam of the ether type or ester type, in order to obtain particularly favorable physical and biopharmaceutical properties, together with a good physiological tolerance. However, other suitable carrier substances meeting the above requirements may also be used. Additionally, medium chain partial glycerides or mixtures of partial glycerides may be introduced into the carrier substance in order to improve the release of lipophile drugs and to affect a regulation of the physical and biopharmaceutical properties of the carrier substance. Also, hydrophilic auxiliary materials may be introduced into the carrier substance in order to improve the release of hydrophile drugs from the carrier substance.

In another aspect of this invention, a one-sided self-adhesive plastic foil in connection with a one-sided self-adhesive foam ring with closed pores is used, whereby the carrier substance is joined to the bottom side of the plastic foil and placed in the opening of the foam ring, in order to obtain a better skin adhesion of the drug plaster in connection with a sufficient occlusion effect as well as a better protection of the carrier substance against thermal and mechanical influences.

The many advantages attained with the invention result predominantly from the fact that the drug release from the bottom of the carrier substance is enhanced by the melting process induced by the skin temperature and that the transfer into the skin occurs from the liquid phase of the carrier substance. As

the carrier substance spreads as a liquid film, the total available complementary skin surface is covered even in its micro topography, contrary to the mechanically more inflexible systems which adhere flat and thus not fully, and also reach the deeper set integumentary system, such as sebaceous glands and sweat glands which present a considerable absorption area. Because of the direct adherence of the liquid phase of the carrier substance, the need for an additional adhesive foil in the absorption area, as is the case with mechanically fixed systems, is eliminated. The tight contact between the liquid phase of the carrier substance and the skin into the micro topographic area also simultaneously reduces the average diffusion distance. Thus, the optimal surface utilization of the available skin absorption area and the reduction of the diffusion distance also provide advantages in the diffusion conditions as compared to the mechanically fixed systems. The specific transport conditions through the skin surface for the various drugs, which occur according to the laws of the so-called 'non-ionic diffusion' are favored overall.

It should be noted that while the carrier substance and the flexible synthetic material may have any shape, they are preferably disk-shaped.

The effects obtained with the successively melting carrier substance disk are comparable to the external application of liquid or viscous preparations, such as salves and sprays, or the internal use of stomach gels or suppositories. However, contrary to the application of salves and sprays, there is no drying of the carrier substance due to evaporation and thus a reduction of the dissolution conditions. Because of its cover, the plaster system much rather creates a moist chamber, which in turn improves the penetration of the medication by increasing the hydration of the arid stratum corneum.

As it is possible to produce for each drug specific galenically optimal carrier substance disks, depending on its physical chemical properties, the system is--with a constant basic configuration--versatile and technologically simple. Contrary to the dermal application of salves, gels and sprays, the system delivers exact dosages. There is also no danger of contamination or loss of medication by outside influences.

As no mechanical component, such as membranes or adhesive foil, is applied between the carrier substance and the skin, there is also no mechanical irritation by friction from this source. While muscular motions or temporary surface changes in the adhesive area, e.g. due to breathing movements in the thorax area, can--in mechanical systems--interfere with the adhesive quality of the adhesive foil or cause a constant mechanical irritation, this effect is rather advantageous with the carrier substance disk, the bottom surface of which is always present as a liquid phase, as it favors the distribution and thus produces a surface increase into the micro topography of the skin, similar to an application of salve.

As the production of the carrier disk, e.g. by simple moulding or pressing, as in the production of suppositories, is less costly than the production of exactly dosed polymer matrices or membrane systems, it is also possible to reduce production costs using the present invention.

Furthermore, it is also possible to include into the carrier disk, apart from homogeneously distributed drugs, pharmaceutically-technically restrained formulations, which have an independently release characteristic, so that a rapid as well as a delayed absorption component can be simultaneously realized in the system. Another possibility for the control of varying release characteristics is the application of several carrier substance disks with varying melting behavior.

Due to the partial penetration of the carrier substance into the pores of the flexible elements, a firm contact between the two components is assured, so that, even with possible damage to the carrier substance disk in the solid state, it does not separate fully or in part from the flexible element. The flexible element also assures, independent from the position of the plaster application, a constant adhesion and thus a firm contact between the carrier substance disk and the skin surface.

Other effects can be attained through the skin temperature, which controls the speed of the melting process. Thus, with a raised skin temperature, e.g. during a fever condition, the melting process and the thus resulting drug release is speeded up. With falling skin temperature, e.g. caused by the transdermally released drug with antipyretic properties, the release speed is again reduced. Such a process corresponds to a direct biological feedback with opposite control effect on the medication release.

Various aspects of the present invention are illustrated in the figures, whereby the examples illustrate the invention, without restricting the same.

The medication is in the carrier substance (1), produced as flat disk. This, in turn, is attached to the bottom side of a porous and flexible synthetic material disk, whereby parts of the carrier substance penetrate into the pores of the synthetic material disk. The latter effect is particularly shown in the partial enlargement of the cross section in **FIG. 3**. The carrier substance disk and the synthetic material disk are located in a housing (3), closed on top, serving as cover layer, which has a circular rim (4). The inside of the housing, as well as the bottom side of the rim are provided with an adhesive layer (5). The adhesive layer inside the housing is used for attaching the synthetic material disk, the adhesive layer of the rim is used for attaching the plaster to the skin surface.

The open lower side of the housing with the carrier substance disk is firmly closed off by a removable foil (6) which sticks to the rim. The foil has dimensions which fully cover the total lower surface including adhesive rim. On one side, a part of the foil protrudes beyond the adhesive rim (7). This part provides for an easy pulling off of the foil from the adhesive surface. Shown in **FIG. 3** is, apart from the mechanical connection between carrier substance disk and synthetic material disk by the penetration of the carrier substance into the pores of the synthetic material disk, also, schematically, the distribution of the liquid phase of the carrier substance on the irregularly structured micro topography of the skin surface (8).

In the modification of the basic system, as shown in **FIGS. 4 and 5**, the top side of the housing is level. The top side of the housing consists of an occlusive plastic foil (3), which is provided with an adhesive layer (5) along its bottom side. In the center part of the lower side of the occlusive plastic foil, the upper side of the synthetic material disk (1) is glued on, whereby this upper part of the synthetic material disk is constructed as mechanical barrier (9), which prevents the diffusion of the drugs into the adhesive zone of the occlusive plastic foil. Glued to the outer area of the lower side of the plastic foil is a circular foam ring (1) made of closed pore polymer material, which, in turn, has an adhesive layer (11) on its lower side. This adhesive layer is used for attaching the medicinal plaster to the skin. The synthetic material disk containing the carrier substance (1) is located in the central opening of the foam ring (10). On the lower side of the synthetic material disk, facing the skin surface, there is a mechanically sealed protective foil (6) with the dimension of the total diameter of the plaster, which is circularly connected to the rim of the adhesive layer of the foam ring (11) and can be removed before applying to the skin.

Shown in **FIG. 5** is the medicinal plaster in an exploded diagram, which shows the main layers plastic foil (3), foam ring (10), synthetic material disk with carrier substance (1) and removable protective foil (6).

According to the present invention, any drug may be delivered through the present medicinal plaster. However, particularly useful drugs are those which can be absorbed by the skin based upon their physicochemical properties. For example, drugs such as those used in the treatment of high blood pressure or angina pectoris may be used. Such drugs are the so-called calcium antagonists, and .beta.-blockers, which are well-known to those skilled in the art.

The medicinal plaster of the present invention may be used on the surface of any mammalian skin such as a dog or cat but, preferably human skin. The medicinal plaster is attached to the skin and is charged with an effective amount of medication for the intended purpose. Of course, the precise amount of medication used will vary depending upon the mammalian or human body weight, the nature of the drug and the nature of the treatment. However, such amounts would be known to those skilled in the art in view of the above disclosure.

Having now fully described this invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

The term "adepts solidus" is a synonym for "solid fats".

The term "solid fats" comprises triglycerides of saturated carbon acids having 10 to 18 carbon atoms in the chain.

The term "medium chain length partial glycerides" comprises mono- and diglycerides of saturated and/or unsaturated carbon acids having 8 to 12 carbon atoms in the chain.

The term "gelatin" comprises a hydrolysis product of ossein.

The term "polyurethan foam of the ether/ester type" comprises reaction products of polyfunctional isocyanates with polyesters or polyethers containing hydroxyl groups.

United States Patent 5,120,710

Liedtke, June 9, 1992

Oral lipid medicinal composition

Abstract. To improve the absorption of active ingredients, which are not adequately bio-available on oral administration, an oral lipid medicinal composition is formed by combining a semi-solid, lipophilic component with a solid, water-soluble component. The semi-solid component is a homogeneous lipid mixture that exists as a hard fat with thermally reversible fat/liquid melting property, at least 95% of which is present in the liquid aggregate state below the body temperature of 37.degree. C. and comprises monoacyl-, diacyl-, and triacylglycerides of saturated vegetable fatty acids with chain lengths ranging from 6 to 18 carbon atoms, preferably comprising a mixture of 40 to 60% monoacyl- and diacylglycerides and 40 to 60% triacylglycerides, in which the active ingredients are either dissolved, suspended or emulsified. The solid component comprises a non-diffusible, water-soluble shell which is not chemically bonded to the lipid compound and envelops the entire lipid compound and is preferably made of gelatin or starch. The use of protease inhibitors in the lipid mixture can improve the permeation conditions for peptides and proteins. The use of highly disperse silicon dioxide can stabilize the suspension formulations. Physical-chemical and biochemical aspects of the oral lipid medicinal form yield improvements for the absorption of drugs that are not adequately bio-available on oral administration.

Claims

1. An oral lipid medicinal composition, comprising a semi-solid, lipophilic component and a solid, water-soluble component, wherein said semi-solid component is a homogeneous lipid mixture that exists as a hard fat with a thermally reversible solid/liquid melting property, and at least 95% of which is present in the liquid aggregate state below the body temperature of 37.degree. C., and comprises monoacyl-, diacyl-, and triacylglycerides of saturated vegetable fatty acids with chain lengths ranging from 6 to 18 carbon atoms, in which a protease inhibitor and an effective amount of an active ingredient which has a peptide or protein structure are either dissolved, suspended or emulsified, and wherein said solid component comprises a non-diffusible, water-soluble shell that envelops the entire semi-solid component, is not chemically bonded to the semi-solid component, and is made of a hard or soft gelatin or starch.
2. The composition of claim 1, wherein said active ingredient is insulin.
3. The composition of claim 1, wherein said semi-solid component comprises 40 to 60% monoacylglycerides and diacylglycerides and 40 to 60% triacylglycerides.
4. The composition of claim 1, wherein said watersoluble shell further contains a protective layer against gastric juice.
5. The composition of claim 1, wherein the percentages of fatty acids that are contained in the entire lipid mixture are 10-18% for caprylic acid, 5-15% for capric acid, 45-55% for lauric acid, 9-15% for myristic acid, 3-10% for palmitic acid, and 3-10% for stearic acid, and said fatty acids are present as components of monoacyl-, diacyl- or triacylglycerides.
6. The composition of claim 1, wherein said protease inhibitor is aprotinin.
7. The composition of claim 1, wherein 1.5% of highly disperse silicon dioxide in hydrophilic or hydrophobic form is added to said lipid compound.
8. The composition of claim 1, wherein said active ingredient is selected from the group consisting of insulin, calcitonin, atrial natriuretic peptide (ANP), interferon, somatostatin, and enkephalin.
9. The composition of claim 1, wherein 95% of said lipid mixture is present in the liquid aggregate state at the physiological human body temperature of 37.degree. C.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to oral lipid medicinal compositions, which improve the absorption of active ingredients, which are not adequately bio-available on oral administration, and methods for preparing such compositions.

2. Discussion of the Invention

It is well known that on oral administration of oral drugs, that have been available to date, numerous drugs cannot be adequately absorbed. Among others, such drugs include various antibiotics and in particular drugs with a peptide or protein structure. To date, the latter can be effectively applied only parenterally, since following oral administration, they become biochemically inactive already in the gastrointestinal tract, before they even reach the site of absorption. The best known example is the blood sugar reducing proteohormone insulin.

Especially in the case of rectal and dermal applications, it is well known that carrier substrates, which contain, among other things, different mixtures of lipids, can lead to significant differences in drug absorption. Lipid mixtures of this kind have, as a function of the kind and proportion of added lipids (i.e., esters of glycerin and short, medium, or long chain, saturated or unsaturated fatty acids, which in turn can also be present as monoacylglycerides and monoacidic or mixed acid di- and triacylglycerides), a corresponding different solubility behavior and also different solubility behavior for the active ingredients. Consequently, quantitative and qualitative different relations of lipid mixtures can have a significant impact on drug absorption. In accordance with the resulting hydrophilic/lipophilic ratios, the active ingredients must also be worked into the lipid compounds in a specific pharmaceutical format.

However, rectal and dermal applications do not fulfill the prerequisites of fast bio-availability in all cases, as desired or required by some drugs, due to their specific pharmacokinetic profiles and anatomical peculiarities. Tests to apply oral formulations based exclusively on fats, in particular with triacylglycerides as tablets, compressed fat granules or smaller fat globules (fat pellets) with high melting points in order to attain delayed release through diffusion or enzymatic erosion, have already been known for a long time. However, these formulations require a specific manufacturing technology, are suitable primarily only for lipophilic drugs and exhibit no advantages in bio-availability with respect to the usual oral drug formulations, e.g., hydrophilic tablets. Therefore, they have not found any wide therapeutic use.

Attempts to use so-called liposomes, i.e., preferably with the use of phospholipids, such as, among others, phosphatidylcholine, manufactured smallest spherical lipid particles (nano particles), as a drug-including vehicle, are also known. The manufacture of these particles is technically complicated, and in particular liposomes have significant stability problems.

A commercial alternative is the attempt in the direction of highly disperse particles, containing primarily triacylglyceride particles (micro pellets), which are also present, e.g., as a powder.

Another problem with different fat mixtures is that they can exhibit unstable modifications and thus are sensitive to storage. This applies in particular to fat mixtures, e.g., based on cacao butter. The use of unsaturated fatty acids, such as oleic acid (C18:1), linoleic acid (C18:2) and linolenic acid (C18:3) in fat mixtures can also result in oxidation-induced storage problems with the risk of rancidity. Long chain triacylglycerides also have relatively poor solution and solubility properties and are, therefore, suitable primarily for more lipophilic drugs. In addition, apparently following absorption, they are also transported predominantly over lymphatic paths in the gastrointestines, which is a different pathway for the transport of esters of glycerin and short chain fatty acids. Due to the distinctly lower flux rates in the lymph pathways, this results on the whole in slower absorption. In addition, long chain triacylglycerides of gastrointestinal lipases are hydrolyzed more than medium chain ones.

Thus, there remains a need for improving the absorption of active ingredients, which are not adequately bio-available following oral administration.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide medicinal compositions which result in effective absorption of active ingredients, which are not adequately bio-available on oral administration.

It is another object of the present invention to provide a method for preparing medicinal compositions which result in the effective absorption of active ingredients which are not adequately bio-available on oral administration.

These and other objects, which will become apparent during the course of the following detailed description, have been achieved by oral lipid medicinal composition formed by combining a semi-solid, lipophilic component with a solid, water-soluble component, wherein the semi-solid component is a homogeneous lipid mixture that exists as a hard fat with a thermally reversible solid/liquid melting property and at least 95% of which is present in the liquid aggregate state below the body temperature of 37.degree. C, and comprises monoacyl-, diacyl- and triacylglycerides of saturated vegetable fatty acids with chain lengths ranging from 6 to 18 carbon atoms, preferably comprising a mixture of 40 to 60% monoacyl- and diacylglycerides and 40 to 60% triacylglycerides, in which the active ingredients are either dissolved, suspended or emulsified, and wherein the solid component of the medicinal form comprises a non-diffusible, water-soluble shell that envelops the entire lipid compound, is not chemically bounded to the lipid compound, and is made of a hard or soft gelatin or starch, and can also contain a protective layer against the gastric juice, and a method for preparing such compositions in which the heated liquid active ingredient-containing lipid is poured into a prefabricated shell.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Thus, at least 95% by weight of the lipid compound is present in the liquid aggregate state at the physiological human body temperature of 37.degree. C.

In one embodiment of the invention to further optimize the proportions of fatty acids in the lipid mixture, the ratio of fatty acids that are used in the entire lipid mixture amounts to 10-18% for caprylic acid, 5-15% for capric acid, 45-55% for lauric acid, 9-15% for myristic acid, 3-10% for palmitic acid, and 3-10% for stearic acid, and these fatty acids are present as components of monoacyl-, diacyl- and triacylglycerides.

An example of a mixture for such a lipid formulation, which serves only as further explanation of the invention without restricting it thereto is a composition in which the percentages of the fatty acids added are: 16% caprylic acid, 13% capric acid, 50% lauric acid, 11% myristic acid, 5% palmitic acid and 5% stearic acid, and the percentages of the mono-, di-, and triacylglycerides are monoacylglyceride: 34%; diacylglyceride: 14%; and triacylglyceride: 52%. The fatty acids in the lipid mixture are determined by gas chromatography (GC) by means of the fatty acid methyl esters. Acetylation of the lipid compound leads to glycerides, which can then be directly introduced to the gas chromatograph. The evaluation of the peak of the gas chromatography yields a quantitative picture of the obtained monoacyl-, diacyl- and triacylglycerides, wherein the partial glycerides exhibit acetyl groups.

The proof of the suitable melting behavior of this lipid compound can be determined either by determining the rising melting point, the dropping point or by means of thermoanalysis. In this case, thermoanalysis reproduces the entire melting pattern during the absorption of heat. With thermoanalysis it can be proven with a lipid composition of the aforementioned kind that at approximately 24.degree. C. only a very small portion of the lipid compound is melted, that the bulk of the melting process is at 30.degree. C. and only a small portion melts at 37.degree. C. In contrast, the measurement conducted by comparison of the rising melting point alone shows a value of approximately 36.degree. C. A suitable solid fat index (solid fat content, SFC) for a lipid compound compounded in such a manner can be determined by means of nuclear magnetic resonance measurement. In this manner the particles, which are still solid at specific temperatures, are measured. For example, the lipids in a precision pre-treatment are treated as follows: 3 g of a specimen are melted for 30 minutes at 70.degree. C., stored for 60 minutes at 0.degree. C. and stored for 35 minutes at measurement temperature. A characteristic pattern of the mean value of the solid content resulting from 3 measurements is, for example, for the aforementioned exemplary lipid formulation: 0.degree. C. = 83%,

10.degree. C. = 79%, 20.degree. C - 63%, 25.degree. C. = 45%, 30.degree. C. = 13%, 32.5.degree. C. = 6%, 35.degree. C. = 4%, 37.5.degree. C. = 2%, 40C. = 0%. Therefore, at a temperature of 35.degree. C., 96% of the lipid mixture is almost completely in the liquid state and at 37.5.degree. C., 98% is almost completely in the liquid state, whereas at the normal external storage temperatures said lipid mixture shows physically no fluid properties.

In order to improve the absorption especially of substances with a peptide or protein structure, protease inhibitors, in particular aprotinin, are added, according to another embodiment of the invention, to the lipid compound as another protective substance.

In order to stabilize suspended active ingredients in the lipid composition, in another embodiment of the invention, 1-5% of highly disperse silicon dioxide in the hydrophilic or hydrophobic form is added.

According to another embodiment of the invention, to simplify the commercial manufacturing process, the heated and liquid active ingredient-containing lipid compound is poured directly into prefabricated capsules made of hard or soft gelatin and solidified therein.

To improve the therapy with drugs that to date have been administered primarily only parenterally, especially drugs with a peptide or protein structure such as insulin, calcitonin, atrial natriuretic peptide (ANP), interferon, somatostatin, and encephaline are added, in another embodiment of the invention.

To improve the therapy of drugs which to date have been administered parenterally or were not satisfactorily absorbed when taken orally, antibiotics, in particular cephalosporins, are added according to another embodiment of the invention.

To improve drug therapy by reducing the required dose, thus reducing the potential for side effects, cardiovascularly effective substances such as beta blockers, calcium antagonists and diuretics such as steroid hormones such as estradiol, progesterone, testosterone and cortisol are added in accordance with another embodiment of the invention.

The advantages of the invention result from the fact that the lipid mixture is a thermally reversible solid-fluid system with natural permeation promoting properties, wherein the specific composition of the lipids has good absorptive capacity for both hydrophilic and lipophilic active ingredients. Thus, no additional penetration promoters, so-called chemical enhancers, are required. This also excludes the risk of incompatibility and local damage to the mucus membrane, which can accompany the use of enhancers.

The good hydrophilic-lipophilic ratios also avoid the use of additional ionogenic or non-ionogenic emulsifiers, surfactants or solubility promoters such as polyethylene glycol compounds (PEG). A physiological emulsification of the lipids released in the gastrointestinal tract occurs due to the endogenic bile acids.

The lipid formulations exhibit excellent compatibility and the starting substances originate from natural sources such as coconut and palm seed fats. The lipid mixtures also meet the USP XXI/National Formulary NF XVI, 4th supplement of the monograph for "Hard Fat".

In a test of a lipid formulation compounded in the above described manner for acute oral toxicity (LD.sub.50, according to OECD no. 401) on rats, the acute mean oral LD.sub.50 was over 2,000 mg/kg of body weight of the rat (limit test). In testing the contact sensitization of the test model according to Magnusson & Kligman (according to OECD no. 406) the sensitization test yielded for the same lipid compound =0% (0/20) and was classified as non-irritating and non-sensitizing on the skin of a guinea pig. An acute dermal toxicity on rats (according to OECD no 402) yielded a mean LD.sub.50 dermally over 2,000 mg/kg of body weight (limit test).

Since the lipid formulations contain exclusively saturated fatty acids, they also exhibit good stability during storage with respect to atmospheric oxygen and thus are not subject to the risk of becoming rancid. The solid shell represents another protective measure against oxidation.

Since the active ingredient-containing lipid mixtures exist in the liquid aggregate state in the gastrointestinal tract at body temperature, as confirmed by means of the aforementioned analysis

through thermoanalysis, rising melting point and solid fat index, following the rapid exit from the carrier shell they spread out directly on the mucus membrane. The result is also good concentration gradients, since the lipids are only partially water soluble and can hardly be diluted. This also enhances rapid absorption and the exposure period for inactivation by means of the gastrointestinal lipases and proteases is shortened.

On the other hand, the solid state of the lipid mixture during storage improves the stability of the active ingredients, and pharmaceutical processing formats such as suspensions or emulsions are mechanically stabilized through solidification.

Both the technological processing of the lipid compounds and the introduction of the lipid compound into the solid shell can be performed with the conventional pharmaceutical methods and facilitate economic mass production.

The lipid mixtures used in the oral lipid medicinal preparation also enhance the efficacy of active ingredients with a peptide and protein structure, which to date could be applied only parenterally, in the form of injections. The therapeutic use by administering corresponding active substances to patients in oral form, instead of in injection form, is offered by the present invention. The fact that it is, as a general rule, possible to produce biological effects also via the oral administration route by means of lipid formulation, e.g., for blood sugar-lowering proteohormone insulin, is demonstrated by the following Examples, which serve only to further explain the invention without restricting it to said Examples.

EXAMPLE 1

Insulin was administered perorally to healthy, non-conditioned white mice. To this end, aqueous insulin solutions with insulin concentrations of 100 IU/ml were dispersed at 38.degree. C. in a lipid mixture of the above compounded kind (percentages of the fatty acids: 16% caprylic acid; 13% capric acid; 50% lauric acid; 11% myristic acid; 5% palmitic acid; and 5% stearic acid and percentages of the mono-, di-, and triacylglycerides: 34% monoacylglyceride; 14% diacylglycerides; and 52% triacylglyceride), which was treated with an addition of 3% highly disperse silicon dioxide, emulsified for several minutes with ultrasonics and then hardened. Microscopic rechecking in the smear preparation of the lipid compound and in aqueous suspension preparations that have been dyed twice shows spherical-vesicular complexes of water and oil or complexes of water and oil and water in the aqueous preparation.

Following reheating to 38.degree. C, 0.4ml of the lipid mixtures with varying insulin concentrations, between 9.5 IU and 0.7 IU insulin/kg of body weight, were injected into the stomachs of groups of 3 fasting mice with a peroral plastic catheter. The individual doses were delivered by diluting the insulin starting solutions, through the corresponding addition of another lipid solution. For each active substance group there was a simultaneous separate and equally large control group to which the same volume of insulin-free lipid mixture was administered. Blood was sampled before and 1, 2 and 4 hours following administration through the caudal vein. The blood glucose concentrations were determined by means of reflection densitometry from the whole blood. The results are shown in **TABLE I**.

The peroral application of insulin resulted, both with respect to the values of the control group that were the same over time and the starting values of the active groups, in a significant, reproducible and dosage-dependent lowering of the blood glucose. With orally administered, unmodified, aqueous insulin solutions no corresponding blood sugar-lowering effect could be detected.

EXAMPLE 2

In a human pharmacological test 9 healthy, male subjects received either subtherapeutic insulin doses (regular human insulin), on average 0.2 or 0.4 IU/kg of body weight, or the same lipid formulation without insulin (placebo) orally. To this end, the same hardened insulin lipid emulsion prepared in Example 1 was in hard gelatin capsules. Three subjects each received 16 IU insulin (8 IU/capsules) or 32 IU and 3 subjects received capsules with placebos. All subjects fasted overnight and received, one hour after administration of the capsules, in periods of one hours, 20 g of standardized carbohydrates. The serum insulin concentration was determined by means of radio immunoassay. The results are shown in **TABLE II**.

It is evident from a group comparison of the chronological patterns of the mean insulin serum concentration that the groups with the insulin formulation exhibit higher insulin concentrations than the placebo group and also the two insulin dosages show differences among one another. It can be inferred that the insulin is absorbed in the intestinal tract of these healthy and normally counter-regulating subjects.

It is evident from the two aforementioned Examples that with the subject matter of the invention, even with molecules having a peptide character, which are usually biologically inactivated in the gastrointestinal tract, biological effects can be generated with an oral application.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

United States Patent 5,686,112

Liedtke , November 11, 1997

Single dosage semi-solid topical pharmaceutical forms for transdermal therapy

Abstract. To improve the efficacy and tolerability of customary topical applications for transdermal systemically acting pharmaceutical substances, single dosage topical pharmaceutical forms which are therapeutically exactly ready-to-administer are formed from suitable semi-solid pharmaceutical forms. The topical single doses are specified pharmaceutically with respect to their dose, their topical spreading behaviour and their permeation properties. Several of the topically ready-to-administer single doses are in this case accommodated in a common commercial packaging container. Complex treatments can be developed by means of different individual dosages or alternatively active compound combinations. As pharmacological active compounds, steroids, peptides, various analgesics, local anaesthetics and non-steroidal antirheumatics are employed in particular. The single dosage topical pharmaceutical form is a safe, easy to administer and inexpensive application form which makes possible a more exact topical therapy for systemic administrations than could previously be achieved using conventional topical administration forms.

Claims

1. A molded body, comprising a plurality of separate, measured and detachable dosages, wherein each of said dosages contains a single dosage, ready-to administer semi-solid phase formulation for transdermal therapy.
2. The molded body of claim 1, wherein said pharmaceutical formulation is in creme, emulsion, gel, suspension or ointment form.
3. The molded body of claim 1, wherein said separate chambers are individually air-tightly sealed with a peel-off foil such that each separate chamber can be opened individually.
4. The molded body of claim 1, wherein said single dosage formulation comprises a pharmaceutical vehicle and an active compound.
5. The molded body of claim 4, wherein said active compound has a uniform average crystal size or a mixture of various crystal sizes.
6. The molded body of claim 4, wherein said active compound comprises estrogens, gestagens, glucocorticoids or mixtures thereof.
7. The molded body of claim 4, wherein said active compound comprises a pharmacologically active peptide, protein or mixture thereof.
8. The molded body of claim 4, wherein said active compound comprises insulin, oxytocin, enkephalins and mixtures thereof.
9. The molded body of claim 4, wherein said active compound is selected from the group consisting of analgesics, local anesthetics and mixtures thereof.
10. The molded body of claim 4, wherein said active compound comprises buprenorphine, fentanyl, penzocaine, morphine, lidocaine, prilocaine, mepivacaine and mixtures thereof.
11. The molded body of claim 4, wherein said active compound comprises antirheumatics, antiinflammatories or mixtures thereof.
12. The molded body of claim 4, wherein said active compound comprises indomethacin, diclofenac, etofenamate or mixtures thereof.

13. The molded body of claim 4, wherein said active compound comprises nicotine.
14. The molded body of claim 4, wherein said separate chambers are marked with numerical, colored or symbolic information or instructions relating to a therapeutic treatment scheme.
15. The molded body of claim 4, wherein said active compound is a morphine derivative.

Description

The invention relates to single dosage semi-solid topical pharmaceutical forms for transdermal therapy, in particular for improving the efficacy and tolerability of systemically acting pharmaceutical substances.

It is known that pharmaceutical substances are also applied to the skin. This is mainly carried out to achieve local effects, but in rarer cases also for systemically affecting bodily functions.

The latter is in particular the administration of topical semi-solid pharmaceutical forms, in particular of ointments, gels and creams, but recently preferably the administration of so-called transdermal therapeutic systems, commercially specified plaster systems which are already employed successfully for the treatment of various disorders.

Transdermal therapy with pharmaceutically customary semi-solid topical administration forms, e.g. in the sex steroid field, and also the transdermal administration of nitroglycerine could previously not be therapeutically successful, however, since the administration of these formulations could previously not be adequately directed to the requirements of a systemic transdermal therapy, in particular due to a lack of dosage accuracy and problems with practical handling. Topical administration of nitroglycerine by means of a spray was also commercially unsuccessful.

On the other hand, therapeutic transdermal systems in the meantime found very wide application, in particular in hormone replacement therapy for the treatment of post-menopausal symptoms and osteoporosis and, with nitroglycerine, as a symptomatic treatment of angina pectoris in coronary heart disease. Recent developments in this field are also aimed at the treatment of pain, e.g. transdermal systems containing the analgesic fentanyl, and at curing smokers, e.g. using transdermal nicotine plasters. Various transdermal application areas, e.g. transdermal scopolamine for the treatment of travel sickness and transdermal clonidine for the treatment of hypertension, also led, however, to controversial views on the benefit/risk ratio.

Customary pharmaceutical topical pharmaceutical forms show essentially relatively great inaccuracy in dosage as transdermal systems. Apart from pharmaceutical differences in the formulations themselves, this can mainly be traced back to the hitherto inconvenient and commercially crude administration technique. Thus, in this connection, only very rough and, from a subjective point of view, estimated volumes are administered from the containers, mainly tubes, partly with the aid of spatulas using a measuring scale. The volume dosage is in this case also still carried out by the patients themselves.

This procedure is only suitable, if at all, for relatively unspecific local therapies, e.g. in the treatment of local contusions with analgesics. Significant dosage problems also result with sprays, since with these not only the accurate release of the dose from the container itself, but also the appropriate topical surface coating is problematical. This is partly already caused, inter alia, by poorly controllable atomisation effects in the air, and partly also by ricochet effects on the skin.

Moreover, this type of intervention also requires special adhesive additives, which raise dermatotoxicological questions.

Transdermal systems are substantially more accurate, but on the other hand also very much more complicated and consequently expensive in terms of production. Furthermore, transdermal systems also frequently exhibit skin irritation, which is produced by the skin occlusion of the plaster necessary for this technique. Moreover, the transdermal systems are also designed for relatively long administration periods of several days, often for reasons of cost. The known transdermal systems are also more fixed to given constant active compound liberation rates, which usually approach zero order release kinetics, and thus correspond to the kinetics of an infusion. As is to be expected biologically, with some active compounds this leads to pharmacological habituation reactions. A practical example here is transdermal nitroglycerine, in which this leads to reproducible tachyphylaxis, by which on repeated administration the antianginal effects are reduced even short-term, in spite of a further increased dose,

up to loss of action. For these cases, either undulating first order kinetics or, occasionally, interruptions of therapy in which the patients thus remain untreated, are the present means of choice for restoration of the activity.

For a topical transdermal therapy of systemic disease states, both sufficiently exact local dosage and the type of the administration scheme are thus both to be taken into account.

Lastly, for patient and physician a type of administration is also important which is suitable to carry out in practice and which avoids preparations which are too complex and thus an adequate readiness of the administration form for application. Furthermore, economical aspects with respect to the costs of a pharmaceutical therapy are also important. This applies in particular to chronic administrations.

The invention is based on the object of improving the efficacy and tolerability of topical administration for transdermal therapy for systemically acting pharmaceutical substances.

This object is achieved according to the invention by the pharmaceutical substances being present as therapeutically ready-to-administer topical individual doses of a suitable semi-solid pharmaceutical form, preferably a cream, emulsion, gel, suspension or ointment, or as therapeutically ready-to-administer topical individual doses of a further pharmaceutical modification of the same semi-solid pharmaceutical form, and the therapeutically ready-to-administer topical individual doses being situated in separate containers of a common commercial moulded body, which simultaneously serves as a pack for several therapeutically ready-to-administer topical individual doses, it being possible for the active compounds to be present in the therapeutically ready-to-administer topical individual doses either in various dosages, on their own, or in active compound combinations.

To improve the efficacy and tolerability of transdermal administrations of a systemic treatment, the active compounds contained in the pharmaceutical vehicle can in this case be present either in a specific average uniform crystal size or alternatively in mixtures having various crystal sizes.

To improve the efficacy and tolerability of transdermal administrations of a systemic treatment with steroids, in a further embodiment of the invention, as active compounds, oestrogens and gestagens or glucocorticoids are present as individual substances or in combinations in the single dosage topical pharmaceutical form.

To improve the efficacy and tolerability of transdermal administrations of a systemic treatment with peptides, in a further embodiment of the invention pharmacologically active peptides and proteins, in particular insulin, oxytocin or encephalins, are present as individual substances or in combinations in the single dosage topical pharmaceutical form.

To improve the efficacy and tolerability of a transdermal systemic pain or rheumatism treatment, in a further embodiment of the invention analgesics and local anaesthetics such as buprenorphine, fentanyl, penzocaine, morphine and morphine derivatives, lidocaine, prilocaine, mepivacaine or non-steroidal antirheumatics/antiinflammatories such as indomethacin, diclofenac or etofenamate are present as individual substances or in combinations in the single dosage topical pharmaceutical form.

To improve the efficacy and tolerability of a transdermal systemic cure for smokers, in a further embodiment of the invention nicotine is present in the single dosage topical pharmaceutical form.

To improve the handling of the single dosage topical pharmaceutical form further in practice, in a further embodiment of the invention, on the moulded body serving as a common pack, appropriate positions of the topical individual dosages in a treatment scheme are marked with numerical, coloured or symbolic information and instructions.

To improve the administration of the single dosage topical pharmaceutical form further in practice, in a further embodiment of the invention therapeutic single doses for various therapy phases are separately detachable from the commercial moulded body serving as a common pack.

The advantages achieved by the invention are in particular that the known therapeutic advantages of transdermal administration can be assumed, e.g. decreased systemic hepatic first pass effect, but at the same time the previous inaccuracy of customary topical pharmaceutical forms is significantly reduced.

Thus, in a laboratory investigation with 50 manual individual withdrawals from prefilled blister chambers for an oestrogen-containing formulation at an individual filling amount of 0.5 gram, a withdrawal accuracy of the topical formulation with a relative standard deviation of 1.9% could be reproduced (**FIG. 1**). This lies significantly below the limit of 5% demanded of pharmaceuticals on the part of GMP procedure. In contrast, on measurement of the reproducibility of the withdrawal for a conventional topical gel formulation containing oestrogen from a customary tube a relative standard deviation of over 15% was found.

The single dosage topical pharmaceutical form moreover makes possible an individualised and variable procedure. It enables prefinished exact dosage changes and also prefinished and exactly dosed combinations. By this means, in its commercial application it also stands in a greater analogy to the procedure in the case of oral administration forms.

The defined total ratios of the single dosage topical pharmaceutical form which result from the specified physicochemical characteristics of the pharmaceutical form, e.g. physical spreading behaviour on the skin and permeation into the skin, the exact topical individual dose and the given prescription scheme, make possible a significantly more exact effect control, and thus also distinctly higher therapeutic safety than previously, compared to customary topical administrations.

Moreover, the single dosage topical pharmaceutical form is also distinctly more hygienic and can be protected better against microbial effects, both with respect to administration itself and with respect to its storage conditions.

Compared with transdermal plasters, the single dosage topical pharmaceutical form is very inexpensive, which results in particular also from its low formulation costs in mass production. It can moreover be prepared with customary pharmaceutical agents and also under all customary production precautions, e.g. aseptic or sterile preparation, and also with suitable stability.

Compared with commercial transdermal systems, the skin tolerability of the single dosage topical pharmaceutical form is fundamentally better.

Modifications of the single dosage topical pharmaceutical form are programmable by means of the type and embodiment of a treatment scheme which can be fixed to the commercial container, for example different dosages and also active compound combinations being possible at the same time, e.g. of oestrogens and oestrogen-gestagen combinations.

By variations in the distributions of the crystal sizes of the active compound contained in the topical pharmaceutical formulations, different pharmacokinetic profiles, e.g. delayed-release effects, can also be produced by the different permeation and depot behaviour resulting therefrom.

The exemplary embodiment of a treatment pack based on the invention, in this case for a single dosage topical administration for hormone replacement in the case of post-menopausal symptoms, may be mentioned. This example is only intended to illustrate the invention without restricting it thereto. It primarily serves the purpose of presenting a therapeutic possibility and also the degree of specificity which can be achieved with single dosage topical pharmaceutical forms in a transdermal systemic therapy.

EXAMPLE

The topical treatment pack consists of a moulded body made of blister material customary for pharmaceutical purposes serving as the pack pack. An individual moulded body in this case contains 14 hemispherically-shaped chambers serving as individual containers for topical individual doses. These can admit filling materials in the range from 0.1 to 1 gram. The treatment pack for one month in this case comprises 2 of these blister packs in each case having 14 chambers for a 28-day treatment with a daily individual dose. The ready-to-administer therapeutic individual doses of the formulation containing 0.5 gram are situated in the chambers. The individual chambers are numbered continuously from 1 to 28. The blister pack 1 with the chambers 1-14 in this case contains in 0.5 gram in each case of topical vehicle 3 mg in each case of the oestrogen 17.β-estradiol; the blister 2 with the chambers

15-28 in this case contains in 0.5 gram in each case of topical vehicle a combination of 3 mg of the oestrogen 17.beta.-estradiol and 1 mg of the gestagen norethisterone acetate.

BRIEF DESCRIPTION OF DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. 1 graphically shows a comparison of the accuracy of single dosage form blisters.

FIG. 2 illustrates the cutaway view of a treatment pack, with topical individual dosage forms.

FIG. 3 represents the mean estrogen serum concentration after single dose application.

The cutaway view of a treatment pack with topical individual dosages is shown for further illustration in **FIG. 2**, this representation only illustrating the pack without restricting it, however, in its further embodiment.

The individual blister chambers of the treatment pack (1), which contain the topical individual doses, are sealed in an air-tight manner on their tops with a peel-off foil (2) of aluminium. The peel-off foils are in this case attached such that they have flaps (3) on their outer side using which each chamber for an individual dose can also be individually opened. The covering foil can in this case be provided in various positions with figures (4) for each day or alternatively additionally with colour codes for the type of treatment phase. The treatment pack is provided with perforations (5) which enable individual doses to be detached from the complete pack in unopened form.

The therapeutic individual doses contained in the individual chambers are withdrawn daily, also as in a tablet administration scheme, and directly applied to the skin. On account of the specified spreading behaviour of the vehicle, a statistically average skin surface coating also results in this case.

The coating volume of the individual dose containers and the statistically average withdrawal residue is checked in production and taken into account according to production.

Using a single dosage topical pharmaceutical form, a clinical pilot test was carried out on 4 subjects using an oestrogen, estriol. The result is shown in **FIG. 3**. The latter represents the average course of the serum concentration of radioimmunologically measured total estriol over a period of 24 hours after topical application. It turns out from this that, with an individual topical dosage, an increased level of steroid hormone lasting for over 24 hours can be achieved on the skin.

United States Patent 5,496,560

Liedtke, March 5, 1996

Borderline active dosage forms of beta blockers

Abstract. For short-term therapy of transient functional cardiovascular symptoms, borderline active dosage forms of beta blockers are used which produce in the body only the borderline active concentrations of active ingredient which produce no significant changes in the physiological values in the cardiovascular system under resting conditions for the respective specific beta blocker used and significantly reduce adrenergically induced transient stimulation effects. Oral, transdermal, or topical dosage forms are particularly advantageous. A differentiated therapy of functional symptoms which does not exist with the customary dosage forms of beta blockers designed for long-term therapies is possible. Both the quality of life and the risk-benefit ratio of the beta blockers are improved. The duration of the therapy also does not have to be extended beyond the symptomatically required scale since no rebound danger exists after withdrawal. As an additional and now indication, this also permits the short-term use for the primary therapy of sleep disturbances, within the framework of vegetative syndromes, in particular, within the framework of postmenopausal symptoms.

Claims

1. A method of effecting short-term therapy of transient functional cardiovascular symptoms, comprising administering to a patient in need thereof a borderline active dosage form of beta blockers, which produces in a patient only borderline active concentrations of active agent which produce no

significant changes in physiological values in a cardiovascular system under resting conditions for the beta blocker used and which significantly reduces adrenergically induced transient stimulation effects from a pharmacodynamic standpoint, and

wherein said dosage form is an oral dosage form, containing 10% to 50% of the currently administered lowest oral therapeutic single dose of the respective beta blocker which is given in a chronic therapy, and

further wherein one dosage is administered about every 24 to 52 hours.

2. The method of claim 1, wherein said dosage comprises a hydrophilic beta blocker selected from the group consisting of atenolol, nadolol, and sotalol and which contain as a respective single oral dose for atenolol, a range of 2.5 to 12.5 milligrams; for nadolol, 6 to 30 milligrams; and for sotalol, 8 to 40 milligrams.

3. A method for treating sleep disturbances, comprising administering to a patient in need thereof a borderline active dosage form of beta blockers, which produces in a patient only borderline active concentrations of active agent which produce no significant changes in physiological values in the cardiovascular system under resting conditions for the beta blocker used and which significantly reduces adrenergically induced transient stimulation effects from a pharmacodynamic standpoint, and wherein said dosage form is an oral dosage form, containing 10% to 50% of the currently administered lowest oral therapeutic single dose of the respective beta blocker which is given in a chronic therapy, and further wherein one dose is administered about every 24 to 52 hours.

4. The method of claim 3, wherein said dosage comprises a hydrophilic beta blocker selected from the group consisting of atenolol, nadolol, and sotalol, and which contains as a respective single oral dose for atenolol, a range of 2.5 to 12.5 milligrams; for nadolol, 6 to 30 milligrams; and for sotalol, 8 to 40 milligrams.

5. A method of effecting short-term therapy of transient functional cardiovascular symptoms, comprising administering to a patient in need thereof a borderline active dosage form of beta blockers, which produces in a patient only borderline active concentrations of active agent which produce no significant changes in physiological values in a cardiovascular system under resting conditions for the beta blocker used and which significantly reduces adrenergically induced transient stimulation effects from a pharmacodynamic standpoint, and

wherein said dosage form is a transdermal dosage form, containing such a loading dose of the beta blocker in the transdermal system, which produces a serum concentration in a range of 10% to 50% of the serum concentration which is produced by the lowest therapeutic oral dosage of the respective beta blocker.

6. The method of claim 5, wherein said dosage comprises a hydrophilic beta blocker selected from the group consisting of atenolol, nadolol, and sotalol and which contain as a respective single oral dose for atenolol, a range of 2.5 to 12.5 milligrams; for nadolol, 6 to 30 milligrams; and for sotalol, 8 to 40 milligrams.

7. A method for treating sleep disturbances, comprising administering to a patient in need thereof a borderline active dosage form of beta blockers, which produces in a patient only borderline active concentrations of active agent which produce no significant changes in physiological values in the cardiovascular system under resting conditions for the beta blocker used and which significantly reduces adrenergically induced transient stimulation effects from a pharmacodynamic standpoint, and wherein said dosage form is a transdermal dosage form, containing such a loading dose of the beta blocker in the transdermal system, which produces a serum concentration in the range of 10% to 50% of the serum concentration which is produced by the lowest therapeutic oral dosage of the respective beta blocker.

8. The method of claim 7, wherein said dosage comprises a hydrophilic beta blocker selected from the group consisting of atenolol, nadolol, and sotalol, and which contains as a respective single oral dose for atenolol, a range of 2.5 to 12.5 milligrams; for nadolol, 6 to 30 milligrams; and for sotalol, 8 to 40 milligrams.

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention concerns borderline active dosage forms of beta blockers for short-term therapy of transient functional cardiovascular symptoms.

2. Background of the Invention

It is known that the chemical group of beta receptor blockers are part of the standard long-term therapy of manifest cardiovascular disorders such as hypertension and angina pectoris. The application spectrum of beta blockers also includes the following indications: hyperkinetic heart syndrome, migraines, tremors, glaucoma, anxiety syndromes, and withdrawal syndromes. See H. Lydtin & P. Trenkwalder, *New Indications for Therapy with Beta-Receptor Blockers in: Beta-Receptor Blockers*, G. Fischer, Stuttgart, 1991, pp. 58ff, incorporated herein by reference.

Cardiovascular disorders can be subdivided diagnostically into those with pathological manifestations (e.g., angina pectoris based on a manifest coronary heart disorder), and into symptomatic types with only transient pathological-manifestations without a pronounced morphologic basis (e.g., situation-related reactive accelerations of the heart rate through exogenous or endogenous physical or psychological stressors). Also classified within this area, in a broader sense, are, for example, transient cardiac ischemias: so-called silent myocardial ischemic episodes which are not noticed by the patient but can be seen in the EKG. Transient manifestations of this type are also referred to as functional or vegetative symptoms and are based primarily on situationally inadequate reactions of the sympathetic nervous system or the adrenergic neurotransmitters released by it.

However, in principle, this diagnostic subdivision comprises therapeutically different objectives and thus imposes different requirements for the beta blocker therapy which basically must take into account the fact that in the vegetative patients it is a matter of largely organically healthy individuals. Consequently, this includes differences in the desired duration of treatment, in the different level of intensity of the therapeutic effect, and different dosing requirements as well as a different evaluation of the associated therapeutic risk-benefit ratio.

Currently available dosage forms of, as well as dosage schemes with, beta blockers in no way take these therapeutically different requirements into account. Thus, identical dosage forms are used without differentiation for the therapy of transient vegetative symptoms even though they were designed for long-term therapy of manifest cardiovascular disorders. There is merely an attempt to adapt, somewhat superficially (e.g., through recommendations to use the minimum doses in the range), within the framework of the dosage spectrum already available for the manifest and chronic syndromes. Nonetheless, this is still done using the same dosing frequencies.

In symptomatic patients with transient cardiovascular reactions, use of the dosage forms of beta blockers as occurs in the therapy of chronic cardiovascular patients is fundamentally a pharmacodynamically unnecessary overdose, with an increased risk of adverse effects.

The entire spectrum of currently available dosage forms of beta blockers desired for long-term therapy reduces, among other things, the overall physical performance capability and affects, for example, lipid and glucose metabolism. See M. Wickelmayr et al., *Glucose Metabolism and Beta-Blockers, Diuretics and Calcium-Antagonists*, pp. 29-33, in: *Effects of Antihypertensive Treatment on Glucose Metabolism*, International Symposium Buhlerhohe 1988, Thieme, Stuttgart--New York 1990, incorporated herein by reference. Since, pharmacokinetically, these dosage forms already cause complete saturation of adrenergic receptors from the outset, the first dose usually already leads, through competitive displacement of endogenous catecholamine, to a long-lasting change of the resting parameters of the cardiovascular system. This is not merely unnecessary for transient vegetative symptoms, but is in fact harmful.

As a consequence, with administration of these customary dosage forms, patients with transient symptoms must also again be gradually withdrawn from this type of beta blocker therapy in order not to be subject to the risk of cardiovascular withdrawal phenomena--so-called rebounds, such as reactive increases in heart rate. Consequently, this imposes a longer than necessary use of beta blockers for these transient symptoms.

All acutely excessive reactions of the sympathetic nervous system to physical and psychological stressors as well as all vegetative individual symptoms which are embedded in various syndromes are vegetative syndromes. For example, even sleep disturbances can be included among the latter. These seriously stressful vegetative symptoms have, however, not been amenable to beta blocker therapy, because of the inappropriate dosage forms and are consequently treated with other therapies. Thus, the primary therapy of sleep disturbances currently uses drugs which act on the central nervous system,

primarily drugs from the chemical group of benzodiazepines, as well as derivatives of barbituric acid. Such treatments present quite significant disadvantages. The sedative effects are not only pronounced but also clearly extend, as residual effects, into the daytime phases of physical activities. These include excessive daytime sleepiness and reduction of functional reactivity and attentiveness. These substances also have a significant addiction potential. Withdrawal after repeated administration frequently triggers adverse effects and vegetative disorders are even intensified, which the patients then wish to prevent with further continuation of this therapy.

There is as yet no use of beta blockers for primary therapy of sleep disturbances. This is also not unexpected since with the dosage forms of beta blockers currently in use, sleep disturbances and nightmares actually are among the adverse effects of these therapies. These undesirable side effects must however be attributed, among other things, to the excessively persistent cardiovascular effects of the customary dosage forms of beta blockers. In particular, the lipophilic beta blockers, which penetrate the CNS barriers more readily, lead to particularly pronounced sleep disturbances. See A. Wasterland, Central Nervous System Side Effects with Hydrophilic and Lipophilic Beta Blockers, *Eur. J. Clin. Pharmacol.* (1985) 23 (Suppl.) 73-76, incorporated herein by reference.

Such adverse side effects also cannot be improved with customary time-released forms of beta blockers, which, for example, are intended to enable a single daily administration. Instead, side-effects are further worsened with such time-released forms since, for pharmacokinetic reasons, these must be dosed even higher to achieve a prolonged persistence of the cardiovascular effects. Extensions of the effects on the vegetative parameters more sensitive to beta blockers, in particular on cardiac chronotropy, are however unnecessary for vegetative symptoms. Thus, the pharmacokinetic half life of the beta blockers, analytically determined only from the plasma concentration, is far shorter than its pharmacodynamic active period. The demonstrable reductions in the heart rate persist well beyond the pharmacokinetic parameters without any therapeutic consequence having been derived for the vegetative parameters.

Scattered reports in the literature point to the fact that in addition to the central nervous causes, peripheral factors may also be implicated in sleep disturbances. Thus, various sleep disturbances clearly coincide with transient vegetative reactions. In poor sleepers, it is possible to detect, in addition to elevated body temperature caused by the central nervous system, elevated secretion of the catecholamines epinephrine and norepinephrine. See K. Adam, in: I. Hindmarch, H. Ott, Th. Roth (Eds.), *Sleep, Benzodiazepines and Performance*, Springer, Berlin, 1984, 44-53, incorporated herein by reference. Comparable processes also seem to be present within the framework of female menopause. Thus, significantly increased sleep disturbances occur in this phase characterized by numerous vegetative functional disorders, in particular appearing within the framework of characteristic hot flashes. See D. Sturdee & M. Brincaat in: J. Studd, M. Whitehead (Eds.), *The Menopause*, Blackwell, Oxford, 1988, pp. 24-42, incorporated herein by reference.

Adrenergically induced cardiac manifestations such as tachycardia appear to intensify anxiety attacks. The occurrence of transient anxiety symptoms after experimental adrenergic stimulation in healthy subjects, for example, with intravenous isoprenaline, is known in human pharmacology.

Consequently, from the aforementioned aspects, a reduction of excessive adrenergic stimulation temporarily affecting the heart seems possible as a principle not applied to date in sleep disturbances. The point of action here is the blockade of sleep-disrupting stress factors caused by the central nervous system. This occurs in particular through the chronotropic adrenergic cardiac receptors especially sensitive to beta blockers. The reactive increase in heart rate triggered by the central nervous system is thus prevented and, at the same time, a negative reinforcement on the central nervous system is averted by blockade of the cardiac feedback reaction. Consequently, this leads to the interruption of a circuit developing between the central nervous system and the heart.

However, for a suitable therapy of transient vegetative symptoms with beta blockers, only reductions of nonphysiological adrenergic stimulation effects are reasonable with the functional disturbances. In contrast, after these temporary situations subside, persistent long-term effects of the beta blockers on the cardiovascular system, in particular persistent effects on physiological base values of the cardiovascular system, are unnecessary and undesirable. They merely manifest themselves in the reduction of performance and negatively affect the quality of life. Consequently, from a

pharmacological standpoint, only a standby situation is required, whereby the pharmacodynamic effect of the beta blocker dosage form is expressed only under stimulation conditions.

Within the framework of various clinical studies with a transdermal system with the beta blocker mepindolol in angina pectoris patients, it was possible to detect serum concentrations of the beta blocker which were lower by a factor of 5 than is the case with the customary therapeutic doses with customary oral application with this beta blocker. With this extraordinarily low concentration of active ingredient, there were differentiated effects on the heart rate. It turned out, as was objectively demonstrated with continuous 24-hour EKGs, that the maximum increases of the heart rate dropped significantly, but the minimum resting rates remained unchanged. This was also accompanied by a significant reduction in silent myocardial ischemic episodes of these patients, thus an improvement in their continuous cardiac circulation. These effects were also successfully reproduced for even shorter applications, e.g., 12-hour applications. See J. Bonelli, P. Gaza, P. Kirsch, R. K. Liedtke, *Int. J. Clin. Pharmacol. Therap. Toxicol.* 29, 425-430 (1991), incorporated herein by reference.

Thus, the possibility exists to counter functional and transient stimulation phases of the adrenergic system even for a short time without at the same time affecting the basal vegetative homeostasis of the cardiovascular system. In contrast to this, with the use of all dosage forms of beta blockers currently in therapeutic use, even with test subjects with healthy circulation, there are always persistent and significant drops in the physiological resting values of the cardiovascular system, which is associated with a general reduction of physical performance capability.

OBJECTS OF THE INVENTORS

One object of the present invention is to enable short-term therapies of transient functional cardiovascular symptoms with beta blockers and to improve the therapy of functional cardiovascular syndromes as a whole. Other objects will become apparent as the invention becomes better understood with reference to the following summary and detailed description.

SUMMARY OF THE INVENTION

The objects of the present invention are accomplished by providing and using dosage forms of beta blockers which produce in the body only those borderline active concentrations of active ingredient which produce, for the respective specific beta blocker used, no significant changes of the physiological values in the cardiovascular system under resting conditions and significantly reduce adrenergically induced transient stimulation effects from a pharmacodynamic standpoint. The dosage forms may be transdermal or topical dosage forms, etc.

DETAILED DESCRIPTION OF THE INVENTION

To expand the therapy potentials for these borderline active dosage forms of beta blockers, the primary therapy of sleep disturbances within the framework of functional syndromes is added as a new medical indication for beta blockers, whereby this also includes the sleep disturbances within the framework of postmenopausal symptoms.

To accomplish this therapy with the use of technical measures which are simpler to achieve, the beta blocker dosage forms are presented such that they are placed in packages which are provided to obtain borderline active beta blocker concentrations for the treatment of vegetative symptoms, in particular with the ingestion and design characteristics of single doses, each of which produces a therapeutic effect for a plurality of days.

To reduce the proportion of direct central nervous effects, hydrophilic beta blockers in particular are used, preferably atenolol, nadolol, and sotalol.

The advantages obtained with the invention include, in particular, that with these borderline active dosage forms the beta blocker therapy of vegetative symptoms and syndromes can be therapeutically safer and their therapeutic spectrum of application can be expanded. The use of beta blockers, e.g., for the therapy of sleep disturbances in vegetative syndromes, has not been possible in this manner in the past with the prior art dosage forms for beta blockers.

Through the invention borderline active dosage forms of beta blockers, it is also possible in particular to significantly reduce the use of therapies acting on the central nervous system with tranquilizers and barbiturates, which include numerous adverse and residual effects. Even the associated potential for addictive risks with these substances can be reduced.

Compared to customary oral dosage forms of beta blockers, the invention borderline active dosage forms of beta blockers also open the possibility of carrying out short-term therapies with transient vegetative symptoms without the danger of cardiovascular withdrawal phenomena. The borderline active dosage forms of beta blockers thus produce only a reduction of adrenergically stimulated reactions but no persistent effects on basal cardiovascular rest values, as is the case with customary dosage forms of beta blockers.

In particular, compared to customary dosage forms of beta blockers, with the invention borderline active dosage forms of beta blockers the obligation to extend the application phase longer than is therapeutically necessary even in the therapy of transient vegetative symptoms and syndromes is eliminated.

Overall, compared to the customary dosage forms of beta blockers, with the invention borderline active dosage forms of beta blockers, the therapeutic risk-benefit ratio in the treatment of vegetative symptoms is significantly improved, for example, with regard to the performance capability and the quality of life of the patients, with regard to adverse effects on lipid and glucose metabolism, with accompanying problems such as reduced renal function with elderly patients and also in the therapy of child patients.

The dosages of beta blockers useful in the present invention are dependent on the route of administration. Oral dosages for vegetative symptoms preferably are in the range of from 10% to 50% of the currently lowest administered single dose as administered for a chronic use with the respective betablocker, including 15%, 20%, 25%, 30%, 35%, 40% and 45% and all ranges there between. Typical oral single doses are in the range, e.g., for Atenolol: of 2.5 to 12.5 milligrams, for Nadolol: 6 to 30 milligrams and for Sotalol: from 8 to 40 milligrams. These single doses can be administered in dosage intervals from 24 hours to 52 hours to treat vegetative symptoms.

Transdermal applications need higher loading doses for the transdermal system. This is due to the different bioavailability provided by this special route of administration compared to oral application. Transdermal systems do not liberate their complete loading dose. The higher concentration of the loading dose is in transdermal systems technically necessary to induce a suitable thermodynamic drive for the percutaneous diffusion process. In general the transdermal application needs similar dosages as the conventional oral does to induce borderline concentrations. The single loading dose in a transdermal patch is for the betablocker Mepindolol in a range of 5 to 20 milligrams.

A 20 mg Mepindolol loading dose in a transdermal patch provided, for 24 hours, continuous serum concentrations of 0.5-2 nanograms/ml (C. de. Mey et al, Transdermal Delivery of Mepindolol and Propranolol in Normal Man, *Arzneim. Forsch./Drug Res.* 39 (II) 150 g (1989) incorporated herein by reference, compared to a transient peak serum concentration of more than 50 nanograms/ml with the same dosage in a tablet (Krause, W., Schwartzkopff, W., Plasma levels of Mepindolol in Healthy Volunteers after Oral Doses of Mepindolol Sulphate, *Arzneim. Forsch./Drug Res.* 33 (II) 1306 (1983) incorporated herein by reference.

For transdermal forms it is necessary to evaluate the individual loading dose empirically for each betablocker, due to their different physico-chemical properties, according to art accepted techniques. A technical composition suitable for the transdermal betablocker application of mepindolol is described in U.S. Pat. No. 4,765,986 incorporated herein by reference.

Different doses of same oral betablocker forms of the same betablocker are dose related absorbed and produce clear dose-concentration relations, which permit direct comparisons. The duration and the expression of the effect of the betablocker depends on the dose and biological affinity to the receptor. Therefore the invention oral betablocker borderline forms can be manufactured in conventional form according to the state of the pharmaceutical art by an ordinary skilled person in this field. The production of a borderline dose form is the same procedure as for a conventional oral form, but the oral borderline active forms contain only dosages in a range of 10% to 50% of the dosages of the respective

usual oral betablocker form as they are administered for conventional oral use in chronic therapy in manifest diseases.

This application is based on German application P4334919.6 filed Oct. 13, 1993 incorporated herein in its entirety by reference. Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that, within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

United States Patent 5,840,755

Liedtke, November 24, 1998

Method and composition for topical therapy of headaches

Abstract. A composition for topical therapy of headaches, which contains a topical carrier system for intact mammalian skin of forehead or temples or both, which contains a therapeutically effective dose of a local anesthetic for delivery to a skin surface underneath the topical carrier system.

Claims

1. A topical carrier system for topical therapy of headaches for application to intact mammalian forehead or temple skin or both, which comprises a therapeutically effective amount or dose of a local anaesthetic for delivery from said topical carrier system to said mammalian forehead or temple skin or both, wherein said topical carrier system comprises at least one component having around, oval, rectangular or semicircular shape.
2. A method for topical therapy of headaches, which comprises applying a therapeutically effective amount of a local anesthetic from a topical carrier system attached on forehead or temple skin or both of a mammal in need thereof, wherein said topical carrier system comprises at least component having a one round, oval, rectangular or semicircular shape.
3. The topical carrier system of claim 1, wherein said local anaesthetic is an amide group- or ester group-containing local anesthetic.
4. The topical carrier system of claim 1, wherein two or more local anesthetics are used each having different pharmacokinetics.
5. The topical carrier system of claim 1, wherein said local anaesthetic is used in an amount of about 0.5 to 40% by weight based upon the total weight of the composition.
6. The topical carrier system of claim 1, wherein said local anesthetic is selected from the group consisting of lidocaine, tetracaine, prilocaine, bupivacaine, mepivacaine, etidocaine, procaine and benzocaine.
7. The topical carrier system of claim 1, wherein said local anesthetic is lidocaine.
8. The topical carrier system of claim 1, wherein the therapeutically effective amount or dose of local anesthetic used is about 10 mg to 50 mg.
9. The method of claim 2, wherein said local anesthetic is an amide group- or ester group-containing local anesthetic.
10. The method of claim 2, wherein two or more local anesthetics are used, each having different pharmacokinetics.
11. The method of claim 10, wherein said local anaesthetic is used in an amount of 0.5 to 40% by weight based upon the total weight of the composition.
12. The method of claim 2, wherein said mammal is human.
13. The method of claim 2, wherein the local anesthetic used is lidocaine.
14. The method of claim 13, wherein the local anesthetic is used in an amount of 10 mg to 50 mg.

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method and composition for topical therapy of headaches.

2. Description of the Background

It is known that headache symptoms which occur as attacks primarily have neurological and vascular causes, however, psychosomatic stress factors, physical environmental factors, functional or organic spinal column disorders related to stress, stimulation of certain cerebral nerves, and even the abuse of substances such as alcohol, nicotine, and analgesics are also implicated.

These symptoms are presently treated to a great extent with pharmaceuticals, such as systemically active, nonopioid, oral or injectable analgesics and antiphlogistics, partially in combination with psychosomatic or physical therapy. Other treatment methods, such as acupuncture, have also been used in combination with these treatments, acupuncture.

However, the conventional pharmacotherapies as a whole still do not afford sufficiently tolerable and effective forms of treatment. In particular, derivatives of salicylic acid, preferably acetylsalicylic acid, nonsteroidal antiphlogistics, for example, ibuprofen, or aniline derivatives, for example, paracetamol, are used as the pharmacologically active principle (e.g., K. Brune, W. Beck in: M. Zenz, I. Jura (Editors) *Lehrbuch der Schmerztherapie (Manual of Pain Therapy)*, WFG, Stuttgart, 1993, pp. 121-135). For migraines, ergotamine derivatives, different tranquilizers of the benzodiazepine group, are used in addition, as well as Beta-blockers for prophylaxis.

Unfortunately, all systemic headache therapies presently in use have in common a considerable number of side effects. For example, salicylic acid derivatives and nonsteroidal antiphlogistics are associated with considerable gastric disorders as a consequence of the antiproliferative active mechanism. Paracetamol is associated with metabolic stress of the liver and kidney functions, especially in prolonged use and with higher doses. The ergotamine derivatives are associated particularly with a very high incidence of gastrointestinal feelings of nausea. The application of these systemic therapies, therefore, is limited by the spectrum in each case of the product-specific, undesirable effects, since systemic interventions involve all organs and organ systems.

A more effective pharmacological principle might be a suitable form of the application of low-dosed local anesthetics. Amide group- and ester group-containing local anesthetics, for example, lidocaine as an amide group-containing local anesthetic, exhibit inhibition of the rapid sodium ion influx into nerve fibers, as a pharmacological activity mechanism. In this way, they block the impulse conduction of the nerve path which, in principle, involves all regional nerve fibers. The sensory and anatomically thinner fibers are more sensitive than the motoric fibers, due to their morphology (G. R. Strichartz (Editor), *Local Anesthetics, Handbook of Experimental Pharmacology*, Vol. 81, Springer, Berlin --New York, 1987). The activity effects can also be differentiated in this way.

A systemic application of local anesthetics might be possible, invasively, by means of injections. However, this option is practically eliminated due to the danger of systemic overdose with, among others, serious cardiac side effects. Direct application of local anesthetics through local injection to the head is technically possible and may be performed in different ways. However, local injections are not only painful, but, moreover, they can never be done directly by the patient. For example, the local surface injection technique involves the so-called neural therapy with trigger points (J. T. Travell, D. G. Simons, *Myofascial Pain and Dysfunction*, Vol. I/II, Williams & Wilkins, Baltimore, 1983) and requires experienced, medical handling and technique. Therefore, it is limited to use in clinically severe disorders. Further, the use of conventional topical formulations, for example, creams, among other things, does not afford either exact dosage or positioning. Moreover, such formulations do not afford continuous penetration over a prolonged period of application.

Thus, a need exists for a method and composition for topical therapy of headaches, which overcome the above disadvantages.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a composition for topical therapy of headaches.

It is also an object of the present invention to provide a method for topical therapy of headaches.

Accordingly, the above objects and others are provided by a composition for topical therapy of headaches, which contains a topical carrier system for application to intact skin of a mammalian forehead or temples or both and a local anesthetic for delivery to a region of skin underneath the topical carrier system.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, a composition is provided for topical therapy of headaches, which contains a topical carrier system for intact mammalian skin of forehead or temples or both, which contains a therapeutically effective dose of a local anesthetic for delivery underneath the topical carrier system.

Although the method and composition of the present invention may be used with any mammal, such as horses, cows, dogs and cats, for example, it is particularly advantageous to use the present invention in conjunction with humans.

In order to improve the efficacy and tolerability of the topical therapy, in one embodiment of the invention, amide group- or ester group-containing local anesthetics are contained in concentration ranges of about 0.5-40% by wt. based upon the total weight of the composition.

In accordance with the present invention, any local anesthetic having amide or ester groups may be used. Such local anesthetics are well known as are synthetic methodologies for preparing the same. For example, lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, etidocaine, procaine and benzocaine may be mentioned. However, any amide group- and/or ester group-containing local anesthetic may be used either alone or in combination with others. Other such local anesthetics are, for example, the esters propoxycaine, hydroxyprocaine, chloroprocaine, ambucaine, metabutoxycaine, proparacaine, paraethoxycaine, butacaine, isobucaine, hexylcaine, piridocaine, piperocaine and cyclomethycaine; or the amides procainamide, dibucaine, pyrrocaine and tolycaine. All of these compounds are known with synthetic methodologies for preparing the same being described in Organic Chemistry of Drug Synthesis, Lednicer et al (Wiley, 1977).

In order to improve the efficacy and tolerability of the therapy, in another embodiment of the invention, two or more local anesthetics with different pharmacokinetics are combined in the topical carrier system used, and these individual substances are present in concentrations such that the total concentration of the two or more active ingredients is not more than 40% by wt. based on the total weight of the composition.

In order to make the therapy more safe and easier to use, in a further embodiment of the invention, the topical carrier system is present in forms which correspond to the special characteristics of the field of application of the skin of the forehead and/or temples of the patient. The external shape of the topical carrier system is, for example, round, oval, rectangular, with concave or convex outer shapes, or the carrier system also can be segmented by the user into appropriate shapes, with or without additional aides.

One particular advantage which can be achieved with the present invention arises from the fact that a noninvasive and local treatment option for symptoms of headache is presented for the first time with this topical carrier system described herein.

Further, topical therapy with local anesthetics in the present topical carrier system makes possible a locally targeted and prolonged therapeutically effective treatment of the terminal and functionally interlinked nerve paths in the area of the head.

Since this area also has good cutaneous absorption capacity, topical doses which are very low can also be used. Systemic danger, as is present with customary oral or injectable analgesics and antiphlogistics, is thereby avoided, because the local anesthetics, for example, lidocaine, are metabolized to a large extent in the delayed cutaneous absorption, so that no systemic activity levels appear with corresponding organ stresses.

The therapy can be managed and maintained with low doses, and as needed, can be interrupted by removal of the carrier.

Generally, although conventional dosages of local anesthetics may be used, it is preferred that the therapeutically effective topical amount of local anesthetic in the carrier, be for lidocaine, for example, in the range of about 10 mg to 50 mg for delivery to the intact skin over a span of about 12 to 36 hours, at a rate in the range of about 0.05 to 1 mg/cm² per hour.

Therefore, the topical therapy of headaches, in accordance with the present invention, has no systemic side effects such as systemic analgesic or antiphlogistic therapies, because a prior active ingredient distribution through the entire body which stresses the other organs and organ systems is avoided. In addition, local anesthetics also exhibit good local tissue tolerability.

As examples of technically suitable designs of a topical carrier system for the skin of the forehead and temples which may be used with local anesthetics in accordance with the present invention, the descriptions of the technical carrier systems in U.S. Pat. No. 4,765,986, EP 0,205,974, DE P3716575.5-45, and DE P3811564.6-45 are cited, without, however, limiting the invention in any way to these described techniques. U.S. Pat. No. 4,765,986 is incorporated herein in the entirety by reference.

Additionally, since the topical carrier system is in a form suitable for the forehead and/or temples, the external shape of the topical carrier system is round, oval, rectangular or semicircular, with concave or convex external shapes. Alternatively, the carrier system can be segmented by the user into appropriate shapes, with or without additional aids.

Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made to the above-described embodiments without departing from the spirit and the scope of the present invention.

United States Patent 5,863,941

Liedtke, January 26, 1999

Method and composition of a topical treatment of inner ear and labyrinth symptoms

Abstract. Periauricularly administered topical therapy with a carrier system containing local anesthetics is a new and effective treatment of disorders of the inner ear and labyrinth, which has a low incidence of side effects. The use of this type of therapy applies especially to a non-invasive topical treatment of tinnitus, vertigo, lack of balance, and nausea.

Claims

1. A method for treating pathological symptoms of the inner ear and labyrinth of a mammal, comprising administering to a periauricular region thereof a topical carrier system which comprises a carrier substance and a therapeutically effective amount of a local anesthetic, said local anesthetic being present in a concentration of about 0.5% to 40% by weight of said carrier substance.
2. The method of claim 1, wherein said pathological symptoms comprise indications for the use of a periauricularly administered topical carrier system which comprises a local anesthetic.
3. The method of claim 2, wherein said indications comprise tinnitus, vertigo, lack of balance, kinetoses and nausea.
4. The method of claim 1, wherein said local anesthetic is an amide- or ester-type anesthetic.
5. The method of claim 4, wherein said amide- or ester-type anesthetic is selected from the group consisting of lidocaine, tetracaine, prilocaine, bupivacaine, mepivacaine, procaine and benzocaine, and wherein said anesthetic is present in a concentration of 0.5% to 40% by weight of said carrier substance.
6. The method of claim 1, wherein said local anesthetic comprises at least two local anesthetics, and wherein the total concentration of said at least two local anesthetics does not exceed 40% by weight of said carrier substance.
7. The method of claim 6, wherein at least one of said at least two local anesthetics is an amide- or an ester-type anesthetic selected from the group consisting of lidocaine, tetracaine, prilocaine, bupivacaine, mepivacaine, procaine and benzocaine.
8. The method of claim 1, wherein said local anesthetic comprises lidocaine, and wherein said therapeutically effective amount comprises 10-50 mg, and wherein said therapeutically effective amount is delivered to the intact skin at a rate of 0.05-1 mg/cm² per hour.

9. The method of claim 1, wherein said topical carrier system comprises a shape that may be round, oval, angular, or crescent-shaped and may be concave or convex, and wherein said carrier system may be cut by a user with or without additional aid into an appropriate shape.

10. A method for preventing pathological symptoms of the inner ear and labyrinth in a mammal, comprising administering to the periauricular region a topical carrier system which comprises a carrier substance in an effective amount of a local anesthetic, wherein said local anesthetic is present in an amount of about 0.5% to 40% by weight of said carrier substance.

11. The method of claim 1, wherein said mammal is a human.

12. The method of claim 1, wherein said local anesthetic is present in an amount of about 0.5% to 30% by weight.

13. The method of claim 12, wherein said local anesthetic is present in an amount of about 0.5 to 20% by weight.

14. The method of claim 13, wherein said local anesthetic is present in an amount of about 0.5 to 10% by weight.

15. The method of claim 10, wherein said mammal is a human.

16. The method of claim 10, wherein said local anesthetic is present in an amount of about 0.5 to 30% by weight.

17. The method of claim 16, wherein said local anesthetic is present in an amount of about 0.5 to 20% by weight.

18. The method of claim 17, wherein said local anesthetic is present in an amount of about 0.5 to 10% by weight.

BACKGROUND OF THE INVENTION

1. Field of the Invention:

The subject of this invention relates to a method and composition of a non-invasive, topical treatment and prevention of pathological symptoms of the inner ear and labyrinth, in particular of tinnitus, vertigo, lack of balance, and nausea.

2. Discussion of the Background:

It is known that in the majority of cases, persistent tinnitus and vertigo, accompanied by a lack of balance and nausea, are due to a disorder or disease of the organs of the inner ear or of the auditory nerves. Tinnitus may occur both in the low-frequency and in the high-frequency range; in the low-frequency range, it occurs especially in the presence of disorders of the auditory canal and the middle ear, in the high-frequency, mainly in the presence of disorders of the labyrinth. These persistent symptoms have an extremely negative effect on those affected. One characteristic complex of symptoms, which includes tinnitus, vertigo and lack of balance, possibly in association with nystagmus, hearing impairment and vomiting, is seen, for example, in Meniere's disease. The sudden attacks of the symptoms may be attributable to vasomotor disorders of labyrinth vessels or temporary disorders of the secretion and composition of the labyrinthine liquor. Under the influence of permanent tinnitus and impaired hearing, the persons affected often become irritable, they suffer from anxiety, and, in some cases, develop considerable psychosomatic problems as this illness proceeds.

The therapeutic methods used so far to treat these problems are not sufficiently effective. If it is not possible to identify an underlying disease, only symptomatic measures, such as stimulus deprivation, rest and pharmacological sedation, can be taken. The pharmacological principle frequently used for this purpose is the orally administered dimenhydrinate which has a sedative effect. Scopolamine, a parasympatholytic agent, may also be used; however, this agent is primarily used to treat the pathophysiologically associated phenomenon of motion-induced nausea, i.e., kinetosis, which develops on exposure to externally moving objects. This sickness is also known as motion or sea sickness and is associated with vegetative phenomena, mainly with nausea. In systemic therapy, scopolamine is also administered by transdermal route (Y. W. Chien, *Novel Drug Delivery Systems, Drugs and the Pharmaceutical Sciences*, Vol. 14, 1982, Marcel Decker, New York), which, when compared to the intramuscular administration of scopolamine, results in a lower and more uniform blood concentration in the body. In spite of this, however, the typical undesirable side effects of scopolamine, in particular, impaired vision, very dry mouth, changes in the ability to concentrate, and somnolence, are observed. The undesirable side effect mentioned last is, among other things, also present after an oral

administration of dimenhydrinate which is also used to treat kinetoses but which is less effective. Thus, overall, the administration of scopolamine as a therapeutic principle is very restricted indeed.

In contrast, the appropriate use of local anesthetics in low doses represents a more effective pharmacological approach. A systemic administration, however, is generally possible by means of injection which as such is undesirable and which, in addition, cannot be used due to the fact that it poses the risk of a systemic overdose with serious cardiac side effects. A direct administration by injection or liquid infusion of local anesthetics to the labyrinthine apparatus of the inner ear itself is technically practically impossible; furthermore, this would carry the risk of ototoxic effects.

The pharmacological mechanism of action of local amide and ester anesthetics, e.g., amide-type lidocaine, is to inhibit the rapid sodium ion influx into the fibers of the nerves. In this manner, these anesthetics block the conduction of impulses of the nerve path, which basically includes all regional nerve fibers. Due to their morphology, however, the thinner sensory fibers are more sensitive than motor fibers, which makes it possible to differentiate between various effects. It is also known that intravenous injections of higher doses of lidocaine (T. Gejrot, Atl. Lokalanasthesie [Atlas of Local Anesthesia], pp. 151-152, Thieme, Stuttgart 1970) as well as a blockage of the ganglion cervicothoracicum with procaine have positive effects on the symptoms of Meniere's disease, although these persist only for a limited period of time.

So far, a non-invasive method and composition for the treatment and prevention of pathological symptoms of the inner ear or labyrinth using a topical carrier system has neither been carried out nor described.

The use of topical carrier systems for drug delivery has been reported (see, for example, U.S. Pat. No. 4,765,986 and European Patent No. 0,205,974).

It is known that medicinal effects can be obtained with medicinal plasters or so-called therapeutic plaster systems, designated lately as transdermal therapeutic systems. At present, this type of system is used in connection with the drug scopolamine for kinetosis, nitroglycerine for coronary heart disease and clonidine for hypertension, as well as for transdermally administered estrogens.

Such plaster systems entail diffusion units in which the medications are released by diffusion at controlled rates from a mechanically fixed drug reservoir, usually tissue tolerant polymers. The systems used are currently divided into membrane systems, i.e., membrane plaster and matrix systems. In the membrane systems the drug, after release from the carrier substance, must permeate a membrane, which serves as a control element for the constant absorption rate. Thereby, it is possible to attain a release characteristic, which approximately corresponds to pharmacokinetics of zero order. In matrix systems, the drug stored in depot form diffuses directly from the polymer matrix into the skin.

However, a non-invasive method and composition for the treatment and prevention of pathological symptoms of the inner ear or labyrinth with a periauricularly administered topical carrier system has neither been carried out nor described.

SUMMARY OF THE INVENTION

The first object of this invention is to provide a therapeutic and preventative method and composition for pathological symptoms of the inner ear or labyrinth using a periauricularly administered topical carrier system.

This object is achieved by attaching a periauricularly administered topical carrier system, which contains a therapeutic or preventative dose of a local anesthetic, and a carrier substance, to the intact skin of the periauricular region and by releasing the local anesthetic into the periauricular skin region below the carrier system.

A second object of this invention provides for new indications, such as the treatment of tinnitus, vertigo, lack of balance, kinetoses and nausea, to be treated by a periauricularly administered topical carrier system which contains a local anesthetic.

A third object of this invention provides for the prevention of tinnitus, vertigo, lack of balance, kinetoses and nausea by a periauricularly administered topical carrier system which contains a local anesthetic.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

To improve the efficacy and tolerability of the periauricularly administered treatment, one embodiment of this invention is to provide a therapeutically and preventatively effective method and composition with a periauricularly administered topical carrier system having a local anesthetic and a carrier substance. The carrier system provides for topical delivery of the local anesthetic.

The local anesthetic is not particularly limited and may include any local anesthetics known in the art (see, for example, those listed in the Merck Index, 11th ed., 1989 herein incorporated by reference). Preferably, the local anesthetics include amide- or ester-type anesthetics. More preferably, the local anesthetics include lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, procaine and benzocaine. The local anesthetics are present in the carrier substance in a range of concentrations from 0.5% to 40% by weight of the carrier substance; preferably 0.5%-30% by weight of the carrier substance, more preferably 0.5%-20% by weight of the carrier substance, most preferably 0.5%-10% by weight of the carrier substance.

To further improve the efficacy and compatibility of the treatment, another embodiment of this invention provides for at least two; preferably at least three, more preferably four or more local anesthetics with different pharmacokinetics with respect to the pathological symptoms of the inner ear or labyrinth to be combined in the periauricularly administered topical carrier system, with the individual local anesthetics being present in concentrations such that the overall concentration of the local anesthetics in the carrier substance does not exceed 40% by weight of the carrier substance; preferably 30% by weight of the carrier substance, more preferably 20% by weight of the carrier substance, and most preferably up to 10% by weight of the carrier substance.

So far, a treatment of pathological symptoms of the inner ear and labyrinth by means of a carrier system with periauricularly administered local anesthetics has neither been carried out nor described. One advantage that may be obtained from this invention results from the fact that the novel pharmacological and technical combination makes it possible for the first time to treat troublesome symptoms of the inner ear and the labyrinthine organ, for which so far no adequate therapy or preventative method and composition existed, using a non-invasive topical carrier system.

The topical treatment with local anesthetics in a carrier system which is applied to the periauricular region makes it possible to therapeutically influence terminally and functionally interlocking nerve paths in a locally targeted and persistent manner.

Furthermore, since the periauricular region has a good cutaneous absorptive capacity, any dose may be administered; low topical doses are preferred. Systemic risks are avoided since local anesthetics, e.g., lidocaine, are believed to be predominantly metabolized in the course of slow cutaneous absorption so that little or no systemic concentrations of the active substances are measured.

The treatment can be controlled by the administration of any dose; preferably small doses, it has a persistent effect and, if required, it can be interrupted by removing the carrier system.

Preferably the therapeutically effective amount in the carrier comprises, in the case of, e.g., the local anaesthetic Lidocaine, a range of 10 mg to 50 mg, which is delivered to the intact skin over a span of 12 to 36 hours, at a rate in the range of 0.05-1 mg/cm² per hour.

Overall, the periauricularly administered topical treatment also has fewer systemic side effects than systemic therapies, such as diphenhydramine or scopolamine, since the active ingredient is believed not to be distributed throughout the body and since, in addition, local anesthetics are believed to be readily tolerated by the local tissues.

Topical carrier systems, and means of their development, are generally known to those of skill in the art. The carrier system of this invention may additionally contain solvents, inert agents, binders stabilizers, anti-oxidants, adhesives and backing materials. The carrier system of this invention may

additionally contain lubricants and emollients. The carrier system may be in the form of a single or multilayer film or sponge form.

The topical delivery system is not particularly limited and may include at least one each of the following: a backing membrane, a reservoir containing the local anesthetic or anesthetics, a microporous rate-controlling membrane, a hypoallergenic skin contact adhesive, a priming reservoir containing the local anesthetics or anesthetics, and a release or peel-off liner. Alternatively, the local anesthetic is contained in a solid carrier substance, which may be in any shape, which may melt at physiological body temperature, whereby the carrier substance may be affixed, to the bottom side of a porous and flexible synthetic material of approximately the same size and shape and the two joined parts are located in a housing, closed on top and open towards the skin side, which may be attached to the skin.

It is also possible to utilize non-homogeneously dissolving local anesthetics which are absorbed in the carrier substance in pharmaceutical technical depot form in order to provide for delayed release.

The carrier substance may include two or more layers having varying melting behavior that may be applied on top of each other in order to attain a varying successive absorption rate of the same or different local anesthetics.

The carrier substance may be distributed in the pores of the whole synthetic material in order to better retain the full flexibility of the synthetic material.

The synthetic material is not particularly limited but may be provided on its top side with a mechanical barrier layer in order to obtain a better mechanical separation between carrier substance and housing.

The synthetic material may preferably be made of polyurethane foam of the ether type or of the ester type in order to attain particularly favorable physical properties together with a physiological indifference or tolerance.

The carrier substances of solid fats/adepts solidus or mixtures of various solid fats may be preferably introduced into the pores of a synthetic material of polyurethane foam of the ether type or ester type, in order to obtain particularly favorable physical and biopharmaceutical properties together with a good physiological tolerance.

Carrier substances of gelatin or mixtures of gelatin and solid fats are preferably introduced into the pores of a synthetic material or polyurethane foam of the ether type or ester type, in order to obtain particularly favorable physical and biopharmaceutical properties, together with a good physiological tolerance. However, other suitable carrier substances meeting the above requirements may also be used. Additionally, medium chain-length partial glycerides or mixtures of partial glycerides may be introduced into the carrier substance in order to improve the release of lipophile drugs and to affect a regulation of the physical and biopharmaceutical properties of the carrier substance. Also, hydrophilic auxiliary materials may be introduced into the carrier substance in order to improve the release of hydrophilic local anesthetics from the carrier substance.

Alternatively, a one-sided self-adhesive plastic foil in connection with a one-sided self-adhesive foam ring with closed pores is used, whereby the carrier substance is joined to the bottom side of the plastic foil and placed in the opening of the foam ring, in order to obtain a better skin adhesion of the drug plaster in connection with a sufficient occlusion effect as well as a better protection of the carrier substance against thermal and mechanical influences.

The effects obtained with the successively melting carrier substance disk are comparable to the external application of liquid or viscous preparations, such as salves and sprays, or the internal use of stomach gels or suppositories. However, contrary to the application of salves and sprays, there is preferably no drying of the carrier substance due to evaporation and thus no reduction of the dissolution conditions. Because of its cover, the topical carrier system rather creates a moist chamber, which is believed to improve the penetration of the local anesthetic by increasing the hydration of the arid stratum corneum.

As it is possible to produce for each local anesthetic specific galenically optimal carrier substances, depending on its physico-chemical properties, the system has a constant basic configuration that is

versatile and technologically simple. Contrary to the dermal application of salves, gels and sprays, the system preferably delivers exact dosages. There is preferably no danger of contamination or loss of medication by outside influences.

Preferably no mechanical components are present, such as membranes or adhesive foil, applied between the carrier substance and the skin, so that irritation by friction is reduced or eliminated. The bottom surface of carrier substance may be present as a liquid phase, which favors the distribution of the local anesthetic and thus produces a surface area increase into the micro topography of the skin, similar to an application of salve.

As the production of the carrier system and carrier substance, e.g. by simple molding or pressing, as in the production of suppositories, is less costly than the production of exactly dosed polymer matrices or membrane systems, it is also possible to keep production costs low.

Furthermore, it is also possible to include into the carrier system and substance, apart from homogeneously distributed local anesthetics, pharmaceutically-technically restrained formulations, which have an independent release characteristic, so that rapid as well as delayed absorption component can be simultaneously realized in the system. Another possibility for the control of varying release characteristics is the application of several carrier substances with varying melting behavior.

Due to the partial penetration of the carrier substance into the pores of the flexible elements, a firm contact between the two components is preferred, so that, even with possible damage to the carrier substance in the solid state, it does not separate fully or in part from the flexible element. The flexible element also assures, independent from the position of the application, a constant adhesion and thus a firm contact between the carrier system and the skin surface.

The local anesthetic release from the bottom of the carrier substance may be enhanced by the melting process induced by the skin temperature and the transfer into the skin occurs from the liquid phase of the carrier substance. As the carrier substance spreads as a liquid film, the total available complementary skin surface is covered even in its micro topography, contrary to the mechanically more inflexible systems which adhere flat and thus not fully, and also reach the deeper set integumentary system, such as sebaceous glands and sweat glands which present a considerable absorption area. Because of the direct adherence of the liquid phase of the carrier substance, the need for an additional adhesive foil in the absorption area, as is the case with mechanically fixed systems, is eliminated. The tight contact between the liquid phase of the carrier substance and the skin into the micro topographic area also simultaneously reduces the average diffusion distance. Thus, the optimal surface utilization of the available skin absorption area and the reduction of the diffusion distance also provide advantages in the diffusion conditions as compared to the mechanically fixed systems. The specific transport conditions through the skin surface for the various drugs, which are believed to occur according to the laws of the so-called 'non-ionic diffusion' are favored overall.

To ensure that the treatment is safer and can be handled more easily, another embodiment of this invention provides for the periauricular administered topical carrier system to be available in shapes which correspond to the special morphology and anatomy of the periauricular region to which the system is attached. It should be noted that while the carrier substance and the flexible synthetic material may have any shape, they are preferably round, oval, angular, crescent-shaped, concave or convex. Additionally, the user, with or without additional aid, may cut the carrier system into appropriate shapes.

The term "adepts solidus" is a synonym for "solid fats". The term "solid fats" comprises triglycerides of saturated carbon acids having 10 to 18 carbon atoms in the chain.

The term "medium chain length partial glycerides" comprises mono- and diglycerides of saturated and/or unsaturated carbon acids having 8 to 12 carbon atoms in the chain.

The term "gelatin" comprises a hydrolysis product of ossein.

The term "polyurethane foam of the ether/ester type" comprises reaction products of polyfunctional isocyanates with polyesters or polyethers containing hydroxyl groups.

The carrier system may be used on the surface of any mammalian skin such as a dog or cat but, preferably human skin. The carrier system is attached to the skin and is charged with an appropriate amount of local anesthetic that is therapeutically or preventatively effective for the pathological

symptoms of the inner ear or labyrinth such as tinnitus, vertigo, lack of balance, kinetoses and nausea. Of course, the precise amount of local anesthetic will vary depending upon the mammalian or human body weight, the nature of the drug and the nature of the treatment. However, such amounts would be known to those skilled in the art in view of the above disclosure.

As an example of a technically suitable embodiment of a periauricularly administered topical carrier system, reference is made to the descriptions of the technical carrier systems in U.S. Pat. No. 4,765,986 and in the European Patent No. 0,205,974, without, however, restricting the scope of this invention to the techniques described. Further, this application is based upon German Patent Application 195 24 691.8, filed in the German Patent Office on Jul. 6, 1995, the entire contents of which are hereby incorporated by reference.

Having now fully described this invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

United States Patent 5,776,952

Liedtke, July 7, 1998

Method and composition for topical therapy of back pain and muscle tension

Abstract

A composition for topical therapy for symptoms of back pain, muscle tension or myofascial pain or a combination thereof, which comprises a topical carrier system for intact skin of the back or outer synovial membranes or both, which comprises a therapeutic dose of a local anesthetic, and which applies the local anesthetic to a region of skin lying beneath the topical carrier system.

Claims

1. A method for topical therapy for symptoms of back pain, muscle tension or myofascial pain or a combination thereof, which comprises administering to a mammal in need thereof a topical carrier system for intact mammalian skin of the back or outer synovial membranes or both, which topical carrier system comprises an analgesically effective dose of a local anesthetic, whereby the local anesthetic is administered to a region of skin lying beneath the topical carrier system.
2. The method according to claim 1, wherein the local anesthetic is an amide or an ester group-containing local anesthetic.
3. The method according to claim 1, wherein the local anesthetic is selected from the group consisting of lidocaine, tetracaine, prilocaine, bupivacaine, mepivacaine, etidocaine, procaine, benzocaine propoxycaine, hydroxyprocaine, chloroprocaine, ambucaine, metabutoxycaine, proparacaine, paraethoxycaine, butacaine, isobucaine, hexylcaine, piridocaine, piperocaine, cyclomethylcaine, procainamide, dibucaine, pyrrocaine and tolycaine.
4. The method according to claim 1, which comprises administering two or more local anesthetics from said topical carrier system, each having different pharmacokinetics from the other or others.
5. The method according to claim 1, which comprises administering about 0.5-40% by weight of said local anesthetic based upon the weight of the composition.
6. The method according to claim 1, wherein the local anesthetic is lidocaine.
7. The method according to claim 6, wherein the analgesically effective dose is about 10 mg to 50 mg.
8. The method according to claim 1, wherein said topical carrier system has a shape which is round, oval or rectangular.
9. The method according to claim 1, which has concave or convex recesses.
10. The method according to claim 1, which is segmented.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method and composition for topical therapy of back pain and muscle tension.

2. Description of the Background

It is known that back pain, muscle tension, and myofascial pain predominantly have neurological and muscular causes, however, psychosomatic stress factors, physical environmental factors, nonfunctional, active or passive fixation in body posture, deficient movement, functional or organic dysfunction of the spinal column due to stress, for example, intervertebral disk damage, are also implicated.

Approximately 80% of the population with varying frequency, experiences back pain. Back pain is also one of the most important causes of lost work time with all of the attendant economic results. Presently, the symptoms of back pain are predominantly treated pharmacologically with systemically active, nonopioid, oral or injectable analgesics and antiphlogistics, and, in part, in combination with psychosomatic or physical therapy, sometimes also in combination with other methods, such as, acupuncture. The last resort for diseases of the intervertebral disk is surgery.

These pharmacotherapies, however, still do not represent sufficiently tolerable and effective forms of treatment. Presently, derivatives of salicylic acid, preferably, acetylsalicylic acid, nonsteroidal antiphlogistics, for example, ibuprofen, or aniline derivatives, for example, paracetamol, are used as the pharmacological principles (e.g., K. Brune, W. Beck in: M. Zenz, I. Jura (Editors) *Lehrbuch der Schmerztherapie (Manual of Pain Therapy)*, WFG, Stuttgart, 1993, pp. 121-135). Furthermore, central or peripheral muscle relaxants are used, as well as tranquilizers of the benzodiazepine group or different antidepressants.

Unfortunately, all systemic analgesic and also muscle-relaxant therapies have a considerable number of undesirable side effects in common. The salicylic acid derivatives and nonsteroidal antiphlogistics are associated considerably and frequently with gastric disorders as a result of the antiproliferative active mechanism. Paracetamol, with a weaker effect, is associated with metabolic stress of liver and kidney functions, especially when used for a prolonged period of time and at required higher doses. Muscle relaxants are associated in particular with a high rate of sedation and gastrointestinal disorders. Therefore, application of these therapies is limited by the spectrum of undesirable, product-specific effects in each case, because systemic interventions involve all of the organs and the organ systems.

A more effective pharmacological principle might be a suitable form of low-dosed local anesthetics. Amide and ester group-containing local anesthetics, for example, lidocaine of the amide type, exhibit, as a pharmacological active mechanism, an inhibition of the rapid sodium ion influx in nerve fibers. In this manner, the impulse conduction of the nerve path is blocked, which in principle involves all regional nerve fibers. The sensory, anatomically thinner fibers are more sensitive than the motoric fibers due to their morphology (G. R. Strichartz (Editor) *Local Anesthetics, Handbook of Experimental Pharmacology*, Vol. 81, Springer, Berlin-N.Y., 1987). The active effects can also be differentiated in this way.

Systemic application of local anesthetics might be applied invasively by means of injection. However, this option is practically eliminated due to the danger of systemic overdose with, among others, serious cardiac side effects. Direct application of local anesthetics through local injection is technically possible and is performed in different ways. However, local injections are not only painful, but can also never be done directly by the patient. The local surface injection technique involves so-called neural therapy with muscular trigger points and requires experienced medical handling and technique (J. T. Travell, D. G. Simons, *Myofascial Pain and Dysfunction*, Vol. I/II, Williams & Wilkins, Baltimore, 1983). Therefore, this option is limited to use in clinically severe disorders. Further, use of conventional topical formulations, for example, creams, allows neither exact dosage nor continuous penetration over a prolonged period of application.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide an improved method of therapy for back pain, muscle tension and myofascial pain.

It is also an object of the present invention to provide a composition for the treatment of back pain, muscle pain and myofascial pain.

The above objects and others are provided by a composition for topical therapy of symptoms of back pain, muscle tension and myofascial pain, which contains a topical carrier system for intact mammalian

skin of the back or outer synovial membrane, which contains a therapeutically effective amount or dose of a local anesthetic, whereby the local anesthetic is applied to a region of skin lying beneath the topical carrier system.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a topical carrier system, suitable for intact skin of the back or outer synovial membranes of a mammal, which is charged with a therapeutic dose of a local anesthetic, whereby the local anesthetic is applied specifically to the skin region located underneath the topical carrier system.

Generally, the present invention may be used in conjunction with any mammal, such as horses, cows, dogs or cats, however, it is particularly advantageous when used with humans.

To improve efficacy and tolerability of the topical therapy, in a further embodiment of the invention, local anesthetics which are amide group- or ester group-containing are contained, especially lidocaine, tetracaine, bupivacaine, prilocaine, mepivacaine, etidocaine, as well as procaine and benzocaine, and these substances are present in concentration ranges of about 0.5-40% by weight based upon the total weight of the composition.

However, any amide group- and/or ester group-containing local anesthetic may be used either alone or in combination with others. Other such local anesthetics are, for example, the esters propoxycaine, hydroxyprocaine, chloroprocaine, ambucaine, metabutoxycaine, proparacaine, paraethoxycaine, butacaine, isobucaine, hexylcaine, piridocaine, piperocaine and cyclomethycaine; or the amides procainamide, dibucaine, pyrrocaine and tolycaine. All of these compounds are known with synthetic methodologies for preparing the same being described in Organic Chemistry of Drug Synthesis, Lednicer et al (Wiley, 1977).

To improve efficacy and tolerability of the therapy, in another embodiment of the invention, two or more local anesthetics with different pharmacokinetics are combined in the topical carrier system used, and these individual substances are present in such concentrations that the total concentration of the two or more active ingredients is not more than 40% by weight based on the total weight of the composition.

Further, to make the therapy as a whole, safer and more manageable, in a further embodiment of the invention, the topical carrier system is presented in a form which corresponds to the specific application field of back skin or outer synovial membranes. Thus, the external shape of the topical carrier system is round, oval, or rectangular, with concave or convex recesses, or the carrier system can be segmented by the user into appropriate shapes, with or without additional aids.

Quite surprisingly, no therapy of back pain, muscle tension, and myofascial pain, using a carrier system with local anesthetics applied to so-called trigger points, has ever before been described. One advantage which is now achieved by virtue of the present invention is that with this new principle, a noninvasive and local treatment option for symptoms of back pain, muscle tension, and myofascial pain is available for the first time.

The present topical therapy with local anesthetics in a topical carrier system also makes possible a locally targeted and long-term therapeutically effective treatment of the terminal and functionally interlinked nerve paths in the area of the surface skin.

Since this surface area also has good cutaneous absorption capacity, lower topical doses can also be used. Advantageously, systemic danger, as it exists with customary oral or injectable analgesics, antiphlogistics, or muscle relaxants, is avoided, because the local anesthetics, for example, lidocaine, are metabolized to a large extent with delayed cutaneous absorption, so that no systemic activity levels appear with the corresponding organ stresses.

Generally, although conventional dosages of local anesthetics may be used, it is preferred that the therapeutically effective topical amount of local anesthetic in the carrier is, for lidocaine, for example, in the range of about 10 mg to 50 mg for delivery to the intact skin over a span of about 12 to 36 hours

at a rate in the range of about 0.05 to 1 mg/cm² per hour. However, other dosage amounts may be used depending upon the particular local anesthetics used.

The present method and composition are also advantageous in that the therapy can be controlled and maintained with low doses and, as needed, can be interrupted by removal of the carrier.

Hence, the present topical therapy of back pain, muscle tension, and myofascial pain avoids the conventional undesirable side effects such as those exhibited by systemic therapies with, among others, analgesics, antiphlogistics, or muscle relaxants, since the prior distribution of the active ingredient through the entire body which stresses the other organs and organ systems is avoided. In addition, local anesthetics also exhibit good local tissue tolerability.

As examples of technically suitable designs of topical carrier system which may be used with local anesthetics, in accordance with the present invention, for the therapy of symptoms of back pain, muscle tension, and myofascial pain, the technical carrier systems in U.S. Pat. No. 4,765,986, DE P3716575.45, and DE P3811564.45 are noted, without limiting the present invention to these described techniques. U.S. Pat. No. 4,765,986 is incorporated herein in the entirety by reference.

Having described the present invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made to the above-described embodiments without departing from the spirit and scope of the present invention.
