Description

Active ingredient and method for testing an active ingredient

The invention relates to a therapeutic active ingredient for administration to a human or animal body, which active ingredient comprises one of the following chemical compounds or is formed thereby. The therapeutic active ingredient contains an α-hydroxy acid, an α-amino acid, a peptide or a protein.

The invention further relates to a method for testing a therapeutic active ingredient, in which the active ingredient is administered to a test subject or the active ingredient is applied to a tissue sample of the tissue to be treated with the active ingredient.

Therapeutic active ingredients (also referred to hereinafter as active ingredients for short) are used to a great extent in modern medicine for treating human or animal bodies. For the purposes of the invention, therapeutic active ingredients are to be understood to mean substances whose purpose is that of curing diseases or alleviating complaints in the human or animal body. Therapeutic active ingredients are available on the market as drugs, which are a preparation containing the therapeutic active ingredient. Here, use is also made of active ingredients which comprise the chemical constituents listed at the beginning or are formed therefrom. Owing to the complex reactions of the active ingredient in the individual to be treated, comprehensive studies are necessary before introducing active ingredients (drugs) to the market, in order to rule out undesired effects of the active ingredient on the individual to be treated

or to reduce them to a tolerable minimum. These experiments are carried out by means of, inter alia, simulations, animal experiments, and, in the final phase prior to approval of a new drug, also by means of studying the administration of the drug to humans. In the interests of the test subjects for the studies on the human body, the statements which can be made about the mode of action of the drug are, however, limited in that only a limited number of clinical diagnostic methods are available for studying the living body.

It is an object of the invention to provide therapeutic active ingredients which allow a comparatively extensive study prior to final approval of the active ingredient, and to specify methods for testing therapeutic active ingredients which enable comparatively comprehensive studies to be carried out prior to the approval of a drug.

According to the invention, using the active ingredient mentioned at the beginning, this object is achieved by radiolabeling the active ingredient with ^{11}C, wherein the ^{11}C replaces the α-carbon-binding carbon of the carboxyl group of the α-hydroxy acid or of the α-amino acid, or the carbon of the peptide bond of the peptide or of the protein. Thus, the result is that, advantageously, the labeled active ingredient is chemically identical to the active ingredient to be studied, since merely one carbon of the active ingredient is replaced with an ^{11}C, and so, advantageously, the chemical effect of the labeled active ingredient is identical to that of the active ingredient to be studied. Thus, the invention provides an active ingredient whose effect is predictable owing to prior studies of the identical unlabeled active ingredient, but which, by means of an examination

using positron emission tomography (also referred to hereinafter as PET for short) after administration of the drug, makes it possible to describe the mode of action of the active ingredient to be studied.

Thus, the above-stated object is achieved according to the invention by specified methods for testing an active ingredient, wherein the active ingredient with radioactive label is used and the distribution of the active ingredient in the test subject is determined by positron emission tomography (also referred to hereinafter as PET for short). Alternatively, it is also possible for the radio labeled active ingredient to be applied to a tissue sample of the tissue to be treated with the active ingredient. Using positron emission tomography, it is then possible according to the invention to determine the distribution of the active ingredient in the tissue.

For the purposes of the invention, active ingredients or drugs are understood to mean physiologically active agents which bring about a desired change in state during therapeutic treatment of a patient, for example the curing of a disease or the alleviation of complaints. By means of positron emission tomography, it is possible during testing of the active ingredient to establish how it and its metabolites are distributed in the body. This is because positron emission tomography allows the acquisition of a three-dimensional image of the distribution of the positron-emitting substances in the test subject. The findings obtained in this way during testing of an active ingredient can, advantageously, provide possible information about the mode of action and, in particular, the site of action of active ingredients and the metabolization thereof. For example, it is possible to predict adverse effects which come about as a result of the active ingredient accumulating not only in the organ to be treated, but also in other organs. It is also possible

to establish how long an active ingredient takes in order to reach the site of action after intake and how long it acts there.

The method of positron emission tomography is known per se. Typically, this method is carried out as an imaging method for the examination of particular tissues. In the prior art, what are known as tracers or biomarkers, which are similar to substances in the body and therefore behave comparably, are prepared for this purpose. As described in the introduction of a dissertation by Kjerstin Bruus-Jensen of the Technical University of Munich from 2006 ("Entwicklung und Evaluierung neuer Methoden zur Radiomarkierung peptidischer Tracer mit ^{18}F und ^{99M}Tc für die nuklearmedizinische Diagnostik" ("Developing and evaluating new methods for radiolabeling peptide tracers with ^{18}F und ^{99M}Tc for diagnostic nuclear medicine")), it is customary to label, for example, peptides with radioactive fluorine. These can be used for an in vivo examination in the human body, and the aim of this diagnostic method is to gain information about pathological states of the examined tissue in the body. It should be noted that the use of ^{18}F to replace, for example, an OH group in the radiolabeled peptide chemically alters this substance and must take place in a region of the molecule which has a negligible effect on the reaction with the peptide in question in the human body.

In contrast, labeling according to the invention a therapeutic active ingredient with ^{11}C has the advantage that the labeled substance is chemically identical to the substance to be studied. Thus, the statements which can be made by means of PET can be applied, without restriction, to the therapeutic active ingredient to be studied.

Advantageously, the therapeutic active ingredient can come from the group consisting of enzymes or hormones. Advantageously, it is also possible for the therapeutic active ingredient to come from the group consisting of antibodies or antibody fragments. These active ingredients are used as immunoglobulins for treating diseases. Also, it is possible to use antibodies or antibody fragments in the form of what are known as conjugates, and in this case a therapeutically effective molecule of the therapeutic active ingredient is coupled to an antibody or an antibody fragment.

It is also advantageous for the therapeutic active ingredient to be prepared as injectable liquid, as infusible liquid or as inhalant, even if the active ingredient is to be supplied later as, for example, a drug in tablet form or in another differing dosage form. Administration of the active ingredient by injection, infusion or inhalation leads, advantageously, to fast absorption, and so the distribution in the body can be determined comparatively quickly by means of PET after administration of the active ingredient. This is advantageous because the ^{11}C-labeled active ingredients have a short half life, and so, after administration of the active ingredient, there is only a short period of time available for detecting it in the body by means of PET.

The above-stated object is also achieved by a method for testing a therapeutic active ingredient, wherein the active ingredient already described above is used and the distribution of the active ingredient in the test subject is determined by positron emission tomography (PET). The advantages of this method, of providing additional information during testing of therapeutic active ingredients have already been explained. Alternatively, it is, advantageously,

also possible to apply the therapeutic active ingredient to a tissue sample which actually represents the tissue to be treated. Here, too, it is possible to monitor the distribution of the therapeutic active ingredient by means of PET, and, advantageously, this method can be carried out without subjecting a human or animal test subject to stress.

It is advantageous when the distribution of the active ingredient in the test subject or in the tissue can be compared with a reference distribution in order to check the efficacy of the therapy with the active ingredient. The reference distribution can, for example, be values available from the literature which relate to the required concentration and distribution of certain active substance groups in the tissue to be treated. Thus, advantageously, it is possible to make better predictions of the effects of new therapeutic active ingredients if they are dependent on sufficient distribution in the tissue to be treated.

The reference distribution can also be determined by reference experiments in accordance with the method according to the invention. For example, it is possible to establish a concentration of the therapeutic active ingredient in a tissue sample that is required in order to achieve the intended therapeutic outcome. Subsequently, in order to determine dosage guidelines for the therapeutic active ingredient, it is possible to study administration thereof in a human or animal test subject with the goal of achieving the required concentration of the active ingredient in the tissue to be treated of the test subject and of thus determining the required dosage of the drugs.

Further details about the invention are described below with reference to the drawing. The single figure shows an exemplary embodiment of the method according to the invention.

The therapeutic active ingredient with the radioactive ^{11}C-label is prepared in a system 11, which is represented diagramatically by an essential element of said system, a cyclotron 11. After preparation of the active ingredient with label, it is applied close in time to a tissue sample 12 in a first phase of the testing and the distribution is checked by means of PET. This procedure can be repeated several times with modifications until a satisfactory result is achieved. Here, it is possible, for example, to generate a reference value which indicates the distribution the therapeutic active ingredient needs to be in to achieve the desired therapeutic effect in the tissue in question.

In a second phase, the radiolabeled therapeutic agent can be administered to a test animal 13. By means of PET, it is possible, for example, to determine the distribution of the therapeutic agent in the organ of the test animal 13, which contains the tissue to be treated 12. This means that, advantageously, initial statements can be made regarding how the therapeutic active ingredient is distributed in the living organism and whether the information obtained in the first phase can be applied.

In a third phase, the therapeutic active ingredient can then be administered to a human test subject 14. Here, too, the PET-determined values for the distribution can be compared with the reference value determined in the first phase. Also possible are statements with regard to whether the information obtained from phase II of the experiment is applicable to humans.

The preparation of, for example, ^{11}C-labeled amino acids is known per se. For example, J. Bolster et al. describe the labeling of tyrosine in the European Journal of Nuclear Medicine (1986), pages 321 to 324. This method can be used in the same way for the other amino acids present in peptides and proteins. In addition, the amino acids obtained in this way can be incorporated into peptides or proteins by means of customary methods. An α-^{11}C-labeled hydroxy acid can, for example, be synthesized by electrochemical reductive carboxylation of a ketone with incorporation of $^{11}CO_2$.

Claims

1. A therapeutic active ingredient for administration to a human or animal body for the purpose of achieving successful therapeutic treatment, which active ingredient comprises one of the following chemical compounds or is formed thereby,

- an α-hydroxy acid,
- an α-amino acid,
- a peptide or
- a protein,

c h a r a c t e r i z e d i n t h a t

the active ingredient is radiolabeled with ^{11}C, wherein the ^{11}C replaces the α-carbon-binding carbon of the carboxyl group of the α-hydroxy acid or of the α-amino acid, or the carbon of a peptide bond of the peptide or of the protein.

2. The active ingredient as claimed in claim 1,

c h a r a c t e r i z e d i n t h a t

it comes from the group consisting of enzymes or hormones.

3. The active ingredient as claimed in claim 1,

c h a r a c t e r i z e d i n t h a t

it comes from the group consisting of antibodies or of antibody fragments.

4. The active ingredient as claimed in claim 1,

c h a r a c t e r i z e d i n t h a t

it comes from the group consisting of conjugates of antibodies or antibody fragments with a therapeutically effective molecule.

5. The active ingredient as claimed in any of the preceding claims,
c h a r a c t e r i z e d i n t h a t
the active ingredient is prepared as injectable liquid, as infusible liquid or as inhalant.

6. A method for testing a therapeutic active ingredient, in which the active ingredient is administered to a test subject (13, 14) for the purpose of obtaining information about the mode of action of the active ingredient, but not for the purpose of achieving successful therapy of the test subject and not for the purpose of diagnosing tissue states in the test subject,
c h a r a c t e r i z e d i n t h a t
a radiolabeled active ingredient according to claim 1, 2, 3 or 4 is used and the distribution of the active ingredient in the test subject (13, 14) is determined by positron emission tomography.

7. The method as claimed in claim 6,
c h a r a c t e r i z e d i n t h a t
the active ingredient is administered intravenously or by inhalation.

8. A method for testing a therapeutic active ingredient, in which the active ingredient is applied to a tissue sample (12) of the tissue to be treated with the active ingredient,
c h a r a c t e r i z e d i n t h a t
a radiolabeled active ingredient according to claim 1, 2, 3 or 4 is used and the distribution of the active ingredient in the tissue sample (12) is determined by positron emission tomography.

9. The method as claimed in any of claims 6 to 8,
c h a r a c t e r i z e d i n t h a t

the distribution of the active ingredient in the test subject (13, 14) or in the tissue sample (12) is compared with a reference distribution in order to check the efficacy of the therapy with the active ingredient.