Description

This invention relates to a novel use of a fat emulsion containing a compound having prostaglandin E_1 activity. More particularly, it relates to its use for improving picture quality in angiography.

PGE_1 is a known vasodilating agent used in the treatment of vascular diseases, and hypertension, for which it is administered by intravenous injection. Since, when so injected, PGE_1 tends to be inactivated during passage through the lung, fat emulsions of PGE_1 ("lipo.PGE_1") have been developed which protect the PGE_1 from such inactivation, see Korosue et al No Shinkei Geka (1987 Jun), 15(6), 635-640 and EP-A-0097481.

Angiography is a clinical technique for observing the flow of a contrast medium such as an iodine compound injected into a blood vessel in a region by taking pictures of such a flow of contrast medium through the vascular system in the region by X-ray photography, X-ray filming or other means. Angiography is used for diagnostical purposes such as (1) diagnosis on expansion or state of lesion in a blood vessel itself, (2) diagnosis of lesion, or its expansion, in various internal organs and their peripheral tissues from exclusive shadow or infiltrative shadow of the blood vessel, and (3) diagnosis on vascular movement or function by continuous photographing of the flow of contrast medium. For example, contrasting of superior mesenteric arteries is an important contrasting examination which is widely used for making decisions on practicing arterial embolectomy for primary liver cancer, determination of the scope of infiltration of pancreatic cancer, diagnosis on esophageal varices, etc.

Hitherto, angiographic adjuvants have been used for promoting the blood flow in a region where angiography is to be performed. In particular, injection forms of vasodilators such as prostaglandin E_1 - (hereinafter referred to as PGE_1) and nitroglycerin have been used. By increasing the blood flow in the region being examined when performing angiography, they make clear the pictures appearing on the screen or the photographs taken during angiography.

The conventional angiographic adjuvants, however, were short in tolerable duration of sustained administration, making it hard to maintain their efficacy for a long time. It was also necessary to administer them at a high dose for performing long-time angiographical observation or for preventing embolus of fine blood vessels after angiography. Further, administration of the conventional adjuvants is accompanied by certain adverse side effects. For instance, it is reported that PGE_1 injection into superior mesenteric arteries may cause abnormal abdominal symptoms such as abdominal pain, burning sensation, tractional sensation, etc., and variation of blood pressure.

For eliminating these problems, an angiographic adjuvant capable of long-time retention in the system and showing a satisfactory efficacy at a small dose has been desired.

As a result of extensive studies to overcome the above problems, we have found that use of a fat emulsion containing a compound having PGE_1 activities as an angiographic adjuvant for improving picture quality in performing angiography can also improve the efficacy retention time and also has the effect of enabling a decrease of dose and reduced manifestation of side effects in the region to which it is administered.

Thus, the invention provides according to one aspect use, in the manufacture of a diagnostic composition for increasing arterial blood flow during angiography, of a compound having PGE_1 activity characterised in that the composition is in the form of a fat emulsion of the said compound.

According to another aspect the invention provides the use of a compound having PGE_1 activity in the manufacture of a diagnostic fat emulsion for increasing arterial blood flow during angiography.

The present invention also provides according to yet another aspect, a method of improving the clarity of angiographic pictures of a human or animal body, which method comprises taking a picture of a human or animal into which (a) a contrast medium and (b) a fat emulsion containing a compound having PGE_1 activity has been intra-arterially injected.

Preferred embodiments of the invention will now be described.

The compounds having PGE_1 activities present in a composition used in accordance with the present invention are not subject to any particular restrictions provided that they are pharmaceutically acceptable ones and have PGE_1 activities. Typical examples of such compounds are PGE_1 and its derivatives.

The PGE_1 derivatives usable as said compound in this invention may be of any type as far as they have PGE_1 activities and are suited for adaptation as a pharmaceutical agent. Preferred examples of such PGE_1 derivatives are shown, for example, in JP-A-206349/84 (EP-A-0132027) and JP-A-216820/84.

A preferred example of a fat emulsion containing a compound having PGE_1 activities, which constitutes active ingredient of the angiographic adjuvant composition used according to this invention, comprises, as main constituents, 5-50% (W/V) of a vegetable oil (such as soybean oil, sesame oil, castor oil, cottonseed oil, olive oil and the like, among which soybean oil is preferred), 1-50, preferably 5-30 parts by weight of

phospholipid for 100 parts by weight of vegetable oil, a proper quantity of water, and a compound having PGE_1 activities. In addition, the fat emulsion may contain, if necessary, an emulsifying adjuvant (for example, up to 0.3% (W/V) of a fatty acid having 6-22, preferably 12-20 carbon atoms or a pharmaceutically acceptable salt thereof), a stabilizer (for example, 0.5% (W/V), preferably 0.1% (W/V) or less of a cholesterol or 5% (W/V), preferably 1% (W/V) or less of phosphatidic acid), a polymeric substance (for example, 0.1-5, preferably 0.5-1 part by weight of albumin, dextran, vinyl polymer, nonionic surfactant, gelatin, hydroxyethyl starch or the like for 1 part by weight of said compound having PGE_1 activities (such as PGE_1 or its derivatives), and an isotonizing agent (for example, glycerin or glucose). The content of the compound having PGE_1 activities in the fat emulsion can be suitably varied according to the formulation of the emulsion, way of administration and other factors, but it should cover the effective amount which is in the range of 0.2 to 100 µg/ml.

The vegetable oil for use in accordance with the present emulsion is preferably a highly purified soybean oil, more preferably the one (purity: 99.9% or above in terms of total glyceride including tri-, di- and monoglyceride) obtained by further purifying common refined soybean oil by steam distillation.

The phospholipid present in the emulsion composition is a purified phospholipid such as egg yolk lecithin or soybean lecithin, which can be obtained by fractionation using an organic solvent. The desired purified phospholipid can be obtained, for example, by slowly adding, with stirring, acetone to a crude yolk phospholipid dissolved in an cold n-hexaneacetone mixture, collecting the insolubles by filtration, repeating the above operation once more, and removing the solvent by distillation. The product comprises phosphatidylcholine and phosphatidylethanolamine as major costituents and minor amounts of other phospholipids such as phosphatididylinositol, phosphatidylserine and sphingomyelin.

One may use a phospholipid containing substantially no phosphatidylcholine which is prepared by purifying further, purified phospholipid according to the method disclosed in US-A-4684633 (EP-A-0150732).

Fatty acids having 6-22 carbon atoms for use as emulsifying adjuvants are those suitable for use in pharmaceuticals. They may be of either straight chain or branched chain. Most preferred are straight chain fatty acids such as stearic, oleic, linolic, palmitic, linoleic, and myristic acids. The salts of these acids should be physiologically acceptable ones such as, for example, alkali metal salts (sodium salt, potassium salt, etc.) and alkaline earth metal salts (calcium salt, etc.).

The cholesterols or phosphatidic acids usable as stabilizers in the emulsion composition may be of any known type which are capable of pharmaceutical usage.

Suitable polymeric substances for incorporation into the emulsion for use in accordance with this invention are albumin, which should be of the human origin, in view of the problem of antigenicity, and vinyl polymers. Suitable vinyl polymers include polyvinylpyrrolidone.

Suitable nonionic surfactants are polyalkylene glycols (for example, polyethylene glycol having an average molecular weight of 1,000-10,000, preferably 4,000-6,000), polyoxyalkylene copolymers (for example, polyoxyethylene-polyoxypropylene copolymer having an average molecular weight of 1,000-20,000, preferably 6,000-10,000), polyoxyalkylene derivatives of hardened castor oil (for example, hardened castor oil polyoxyethylene-(40)-, or -(20) or -(100) ether), and polyoxyalkylene derivatives of castor oil (for example, castor oil polyoxyethylene-(20), -(40) or -(100) ether).

Glycerin and glucose used as isotonizing agent in the emulsion may be of any origin as far as they are pharmaceutically acceptable.

The fat emulsion used in accordance with the present invention can be prepared in the various ways, a typical example of which is as follows. Predetermined amounts of a vegetable oil (preferably soybean oil), phospholipid, a compound having PGE_1 activities and, if necessary, the afore-mentioned additives are mixed and heated to form a solution. This solution is homogenized by a commonly used type of homogenizer (such as high pressure-jet type or ultra- sonic type homogenizer) to prepare a water-in-oil type dispersion. This dispersion is added with a necessary amount of water and again homogenized by the homogenizer to convert the dispersion into an oil-in-water type emulsion, whereby a desired fat emulsion can be obtained. The thus produced fat emulsion may have, further added to its additives such as a stabilizer, isotonizing agent, etc., if necessary for reasons relating to the preparation process (US-A-4493847, EP-A-097481).

The angiographic adjuvant used in accordance with this invention and comprising the fat emulsion is usually administered intravenously or intraarterially, or through other suitable routes. Usually the adjuvant is administered at a dose of about 1 to 50 µg in terms of active principle, but the dose is variable depending upon the condition of the patient, the region to be examined and other matters.

The angiographic adjuvant used in accordance with this invention can be used during the performance of various modes of angiography, including both arteriography and venography. For example, the use, in

accordance with the invention, of the angiographic adjuvant can be in superior mesenteric arteriography, carotid arteriography, abdominal arteriography, femoral arteriography, pulmonary venography and interior aortography.

ADVANTAGEOUS EFFECT OF THE INVENTION

The angiographic adjuvant when used in accordance with the present invention is capable of long-time retention of its efficacy in living bodies and exhibits the desired action with a small dose. This may be attributed to the following reasoning. Usually PGE_1 is rapidly inactivated upon combining with albumin in the living body, so that when using PGE_1 as an angiographic adjuvant, it is hard to maintain its efficacy for a long time, but in the case of the angiographic adjuvant according to this invention, the adjuvant compound having PGE_1 activities is formulated into a fat emulsion and can be absorbed into the blood vessel through its endothelium in a very stable state, so that it can retain its efficacy for a long time with a small dose.

As described above, use of the angiographic adjuvant in accordance with this invention has the advantage of enabling a decrease of dose, which results in reduced side effects, and also contributes to the prevention of embolus of fine blood vessels after the angiographic operation. Thus, the preparation, in the manufacture of which the compound having PGE_1 activity is used in accordance with this invention, is very useful in the practice of angiography.

EXAMPLES

The present invention is illustrated below in detail with reference to Examples and Test Examples of a preparation according to this invention (referred to therein as "PGE_1 -lipo").

EXAMPLE 1

To 30 g of purified soybean oil were added 3.6 g of yolk phospholipid, 900 μg of PGE_1, 0.15 g of sodium palmitate and 0.15 g of phosphatidic acid. The mixture was heated at 40° to 75°C to form a solution. To the solution was added 200 ml of distilled water, followed by the addition of 7.5 g of glycerin of the official grade (Pharmacopoeia of Japan). The mixture was made up to 300 ml with distilled water for injection at 20° to 40°C and coarsely emulsified by a homomixer.

The coarse emulsion was homogenized by passing it 10 times through a Manton-Gaulin type homogenizer under a first-stage pressure of 120 kg/cm^2 and a total pressure of 500 kg/cm^2. There was obtained a homogenized, finely dispersed fat emulsion containing PGE_1 (This preparation is hereinafter referred to as PGE_1-lipo). The emulsion, 0.2-0.4 μ in average size of dispersed droplets, contained none of the droplets of 1 μ or above in size.

EXAMPLE 2

A fat emulsion was prepared following the same recipe and the same procedure as in Example 1, except that 0.15 g of sodium oleate was used in place of 0.15 g of sodium palmitate and 0.15 g of phosphatidic acid.

TEST EXAMPLES

The effect of the angiographic adjuvant of this invention was tested by superior mesenteric portal venography and measuring the change in blood flow rate through the portal vein.

I. Test method

(1) Subjects

Selected as test subjects were 10 cases (7 men and 3 women, 44-68 in age, average age: 64.4) who have been subjected to abdominal angiography. Diagnoses at the time of practice of angiography confirmed 4 cases of primary liver cancer, 2 cases of metastatic liver cancer, 2 cases of cirrhosis of the liver and 2 cases of pancreas cancer.

(2) Abdominal angiography

After puncturing a femoral artery of each subject, a sheath was inserted into said artery by Seldinger method. Then a catheter for angiography (cobra-shaped, RH Type 5.5F, mfd. by Cook Corp.) in said sheath was passed into the main superior mesenteric artery and a contrast medium (Iopamidol; iodine concentration: 370 mg/l) was injected at a rate of 5 ml/sec for 10 seconds (for a total amount of 50 ml). Pictures were taken on 16 films during a period of 30 seconds after start of injection. Thereafter, an α-cyclodextrin clathrate compound of PGE_1 (hereinafter referred to as PGE_1-CD) or PGE_1-lipo was intraarterially injected into said superior mesenteric artery at a dose of 20 μg in terms of PGE_1 in the case of PGE_1-CD and 10 μg in terms of PGE_1 in the case of PGE_1-lipo, immediately followed by angiographic observation and photographing.

Portal venographical pictures were taken and the change of blood flow rate was measured for the 5 cases to which PGE_1-CD was intraarterially injected after intraarterial injection of contrast medium alone (these cases are hereinafter referred to as case group I) and for another 5 cases to which PGE_1-lipo was intraarterially injected after intraarterial injection of contrast medium alone (these cases are hereinafter referred to as case group II), and these two case groups were subjected to a comparative examination in connection to the following test items.

(3) Test items and test method

(i) Measurement of contrast medium concentration

As an index of concentration of contrast medium in the blood vessel, measurement was made of concentration for the contrasted blood vessels on the films by a Fuji Densitometer 301. Measurement was made at the following three regions: main superior mesenteric vein, main portal vein and right branch of portal vein. The average of the measured values at said three regions was given as the determined value.

(ii) Measurement of blood vessel diameter

The blood vessel diameter in the main portal vein was measured on the contrastradiographic films before and after arterial injection of PGE_1-CD or PGE_1-lipo.

(iii) Measurement of change of branch

Change in improvement of fixing of branch by use of PGE_1-CD or PGE_1-poli in portal venography was examined. Branches on the films were identified in case group I and case group II, and the changes before and after arterial injection of PGE_1-CD or PGE_1-lipo were compared.

(iv) Measurement of change of blood flow rate in portal vein

Change of blood flow rate in portal vein was measured by ultrasonic pulse Doppler method. PGE_1-CD or PGE_1-lipo was arterially injected into the portal vein from the superior mesentric artery, and the blood flow rate in the main portal vein was measured by ultrasonic pulse Doppler method (using a device SSD-650 mfd. by Aloca Co., Ltd.). The blood flow rate was calculated from the measured average flow velocity and the sectional area of the main portal vein determined from the B mode image.

II. Test results

(1) Measurement of contrast medium concentration

The concentrations at the three regions: main superior mesentric vein, main portal vein and right branch of portal vein on the contrastradigraphic films were statistically aggregated. From a comparison of the portal venographical images after arterial injection of PGE_1-CD or PGE_1-lipo with those observed when using contrast medium alone, an increase of contrast medium concentration to a significant degree was noted for both PGE_1-CD and PGE_1-lipo, but there was seen no statistically significant difference between PGE_1-CD and PGE_1-lipo at the doses used in this test ($P < 0.01$). In view of the PGE_1 dose of 20 μg in case of administering PGE_1-CD and 10 μg in case of administering PGE_1-lipo, it was found that PGE_1-lipo can produce the same effect as PGE_1-CD with half the amount of active principle of the latter.

(2) Measurement of blood vessel diameter

The changes of blood vessel diameter in main portal vein were as shown in Table 1 (case group I) and Table 2 (case group II). In both of case groups I and II, a significant expansion of blood vessel diameter by arterial injection of PGE_1-CD or PGE_1-lipo was observed. However, there was seen no statistically significant difference between PGE_1-CD and PGE_1-lipo at the doses used in the present test. This attests to the fact that PGE_1-lipo can produce the same effect as PGE_1-CD by administering half the amount of PGE_1-CD in terms of quantity of active principle.

Table 1

(case group I)		
Case No.	Blood vessel diameter (mm)	
	When contrast medium alone was used	After arterial injection of PGE_1-CD
1	12	16
2	16	18
3	17	19
4	15	17
5	12	15

Table 2

(case group II)		
Case No.	Blood vessel diameter (mm)	
	When contrast medium alone was used	After arterial injection of PGE_1-lipo
1	10	14
2	12	16
3	12	16
4	14	17
5	14	15

(3) Measurement of change in branches

The results of identification of branches in the intrahepatic portal vein by observation of portal venographic pictures were as follows. In the case of case group I, when contrast medium alone was arterially injected, there was 2 cases in which 3 branches could be identified and 3 cases in which 4 branches could be identified. On the other hand, when PGE_1-CD was arterially injection, 4 branches could be identified in all cases and as much as 5 branches could be identified in 2 cases. No change was seen in one case. There was noted an improvement in 4 out of 5 cases.

In the case of case group II, when contrast medium alone was injected, 4 branches could be identified in all 5 cases, and when PGE_1-lipo was used, 5 branches could be identified in 4 cases. An improvement was seen in 4 out of 5 cases. The above results suggest that PGE_1-CD and PGE_1-lipo have the same effect regarding identification of fine intrahepatic portal vein vessels at the dose used in the present test, and this was consistent with the static analyses. It was thus ascertained that PGE_1-lipo can produce the same effect as PGE_1-CD with half the amount of active principle of the latter.

(4) Determination of change in blood flow rate in portal vein

The change of blood flow rate in portal vein was determined by ultrasonic pulse Doppler method, obtaining the results shown below.

In case group I, the blood flow rate in portal vein before arterial injection of PGE_1-CD was 9.5 ± 3.0 x 10^2 ml/min, but one minute after arterial injection of PGE_1-CD, said blood flow rate increased to 16.9 ± 6.8 x 10^2 ml/min. On the other hand, in case group II, the blood flow rate in portal vein before arterial injection of PGE_1-lipo was 8.4 ± 3.1 x 10^2 ml/min, but one minute after arterial injection of PGE_1-lipo, it showed a significant increase to 14.8 ± 4.3 x 10^2 ml/min. This was quite significant in statistical terms, too. Also, it is considered that both PGE_1-CD and PGE_1-lipo have the equal effect at the doses used in the present test, and it was found that PGE_1-lipo can produce the same effect as PGE_1-CD with half the content of active principle of the latter.

(5) Side effects

In superior mesentric arterial injection of PGE_1, certain undesirable abdominal symptoms such as abdominal pain, burning sensation, tractional sensation, etc., and other adverse side effects such as variation of blood pressure have been reported in the past. However, in the 5 cases to which PGE_1-lipo has been injected in the present test, there was none which complained of said abdominal symptoms and also there took place no variation of blood pressure exceeding 20 mmHg.

Claims

1. A method of improving the clarity of angiographie pictures of a human or animal body, which method comprises taking a picture of a human or animal into which (a) a contrast medium and (b) a fat emulsion containing a compound having PGE_1 activity has been injected intra-arterially.

2. Use, in the manufacture of a diagnostic composition for increasing arterial blood flow during angiography, of a compound having PGE_1 activity characterised in that the composition is in the form of a fat emulsion of the said compound.

3. Use of a compound having PGE_1 activity in the manufacture of a diagnostic fat emulsion for increasing arterial blood flow during angiography.

Patentansprüche

1. Verfahren zur Verbesserung der Klarheit von angiographischen Bildern eines menschlichen oder tierischen Körpers, wobei das Verfahren die Aufnahme eines Bildes eines Menschen oder Tieres umfaßt, in den (das) (a) ein Kontrastmedium und (b) eine eine Verbindung mit PGE_1-Aktivität enthaltende Fettemulsion intra-arteriell injiziert wurde.

2. Verwendung einer Verbindung mit PGE_1-Aktivität zur Herstellung einer diagnostischen Zusammensetzung zur Steigerung der arteriellen Durchblutung während einer Angiographie, dadurch gekennzeichnet, daß die Zusammensetzung in Form einer Fettemulsion der Verbindung vorliegt.

3. Verwendung einer Verbindung mit PGE_1-Aktivität zur Herstellung einer diagnostischen Fettemulsion zur Steigerung der artiellen Durchblutung während einer Angiographie.

Revendications

1. Procédé d'amélioration de la clarté d'images angiographiques de corps humain ou animal, selon lequel on réalise une image d'un homme ou d'un animal dans lequel on a injecté par voie intra-artérielle (a) un agent de contraste, et (b) une émulsion grasse d'un composé ayant une activité de PGE_1.

2. Utilisation pour la préparation d'une composition de diagnostic, pour accroître le débit sanguin artériel au cours d'une angiographie, d'un composé ayant une activité de PGE_1, caractérisée en ce que la composition est sous la forme d'une émulsion grasse dudit composé.

(4) Determination of change in blood flow rate in portal vein

The change of blood flow rate in portal vein was determined by ultrasonic pulse Doppler method, obtaining the results shown below.

In case group I, the blood flow rate in portal vein before arterial injection of PGE_1-CD was 9.5 ± 3.0 x 10^2 ml/min, but one minute after arterial injection of PGE_1-CD, said blood flow rate increased to 16.9 ± 6.8 x 10^2 ml/min. On the other hand, in case group II, the blood flow rate in portal vein before arterial injection of PGE_1-lipo was 8.4 ± 3.1 x 10^2 ml/min, but one minute after arterial injection of PGE_1-lipo, it showed a significant increase to 14.8 ± 4.3 x 10^2 ml/min. This was quite significant in statistical terms, too. Also, it is considered that both PGE_1-CD and PGE_1-lipo have the equal effect at the doses used in the present test, and it was found that PGE_1-lipo can produce the same effect as PGE_1-CD with half the content of active principle of the latter.

(5) Side effects

In superior mesentric arterial injection of PGE_1, certain undesirable abdominal symptoms such as abdominal pain, burning sensation, tractional sensation, etc., and other adverse side effects such as variation of blood pressure have been reported in the past. However, in the 5 cases to which PGE_1-lipo has been injected in the present test, there was none which complained of said abdominal symptoms and also there took place no variation of blood pressure exceeding 20 mmHg.

Claims

1. A method of improving the clarity of angiographie pictures of a human or animal body, which method comprises taking a picture of a human or animal into which (a) a contrast medium and (b) a fat emulsion containing a compound having PGE_1 activity has been injected intra-arterially.

2. Use, in the manufacture of a diagnostic composition for increasing arterial blood flow during angiography, of a compound having PGE_1 activity characterised in that the composition is in the form of a fat emulsion of the said compound.

3. Use of a compound having PGE_1 activity in the manufacture of a diagnostic fat emulsion for increasing arterial blood flow during angiography.

Patentansprüche

1. Verfahren zur Verbesserung der Klarheit von angiographischen Bildern eines menschlichen oder tierischen Körpers, wobei das Verfahren die Aufnahme eines Bildes eines Menschen oder Tieres umfaßt, in den (das) (a) ein Kontrastmedium und (b) eine eine Verbindung mit PGE_1-Aktivität enthaltende Fettemulsion intra-arteriell injiziert wurde.

2. Verwendung einer Verbindung mit PGE_1-Aktivität zur Herstellung einer diagnostischen Zusammensetzung zur Steigerung der arteriellen Durchblutung während einer Angiographie, dadurch gekennzeichnet, daß die Zusammensetzung in Form einer Fettemulsion der Verbindung vorliegt.

3. Verwendung einer Verbindung mit PGE_1-Aktivität zur Herstellung einer diagnostischen Fettemulsion zur Steigerung der artiellen Durchblutung während einer Angiographie.

Revendications

1. Procédé d'amélioration de la clarté d'images angiographiques de corps humain ou animal, selon lequel on réalise une image d'un homme ou d'un animal dans lequel on a injecté par voie intra-artérielle (a) un agent de contraste, et (b) une émulsion grasse d'un composé ayant une activité de PGE_1.

2. Utilisation pour la préparation d'une composition de diagnostic, pour accroître le débit sanguin artériel au cours d'une angiographie, d'un composé ayant une activité de PGE_1, caractérisée en ce que la composition est sous la forme d'une émulsion grasse dudit composé.

* C L M S *

3. Utilisation d'un composé ayant une activité de PGE_1, pour la préparation d'une émulsion grasse de diagnostic, pour accroître le débit sanguin artériel au cours d'une angiographie.