Abstract: The invention relates to the use of a peripherally restricted antagonist of an opioid receptor for treating opioid withdrawal syndrome. Preferably, the peripherally restricted antagonist of an opioid receptor is selected from the group consisting of 4,5alpha-Epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)morphinanium iodide and 17-(Cyclopropylmethyl)-4,5alpha-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium iodide.
METHOD FOR TREATING OPIOID WITHDRAWAL SYNDROME

FIELD OF THE INVENTION

The present invention relates to the use of peripherally restricted antagonists of opioid receptors for the treatment of opioid withdrawal syndrome.

BACKGROUND OF THE INVENTION

Regular use of an opioid for any reason rapidly induces a physical dependence. Unpleasant opioid withdrawal syndrome can occur when the opioid is discontinued or rapidly reduced in dosage. Acute opioid withdrawal syndrome can occur following administration of an opioid receptor antagonist such as naloxone or naltrexone. Signs and symptoms of opioid withdrawal syndrome may include: sweating, malaise, anxiety, depression, persistent and intense penile erection in males (priapism), extra sensitivity of the genitals in females, general feeling of heaviness, cramp-like pains in the limbs, yawning and lacrimation, sleep difficulties, cold sweats, chills, severe muscle and bone aches not precipitated by any physical trauma, nausea and vomiting, diarrhea, goose bumps, cramps, fever, painful conditions, muscle spasms in the legs of the user (restless leg syndrome).

Two general approaches are available to facilitate the physical part of opioid withdrawal.

The first approach is to substitute a longer-acting opioid such as methadone or buprenorphine for heroin or another short-acting opioid and then
slowly taper the dose. However, this approach can not be realized in some countries due to legal restriction on the use of methadone or buprenorphine for such purposes.

The second approach is treating extreme anxiety of opioid withdrawal by the use of benzodiazepines. However, benzodiazepines also have a great addiction potential and should be used with care.

Thus, there is the great need in safe agents for the treatment of opioid withdrawal syndrome without side effects like as addiction.

Naloxone and naltrexone are opioid receptor antagonists which capable to block both central and peripheral opioid receptors. Administering naloxone or naltrexone to a subject which regularly used of an opioid for any reason can induce acute opioid withdrawal syndrome in this subject. Surprisingly, we discovered that administering of peripherally restricted antagonists of opioid receptors to a subject which regularly used of an opioid does not induce withdrawal syndrome and, in contrast, is useful for the treatment of the opioid withdrawal syndrome. The peripherally restricted antagonists are capable to block peripheral opioid receptors and do not block central opioid receptors. The examples of peripherally restricted antagonists are quaternary derivatives of naloxone and naltrexone, which block peripheral opioid receptors and do not capable to block central opioid receptors due to decreased transport of quaternary derivatives of naloxone and naltrexone through blood brain barrier.

It is an object of the present invention to provide a method for treating opioid withdrawal syndrome comprising administering to a mammal in need thereof an effective amount of a peripherally restricted antagonist of an opioid receptor.
It is an object of the present invention to provide the use of a peripherally restricted antagonist of an opioid receptor for manufacturing a medicament for the treatment of opioid withdrawal syndrome.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for treating opioid withdrawal syndrome comprising administering to a mammal in need thereof an effective amount of a peripherally restricted antagonist of an opioid receptor. Preferably, the mammal is a human.

As used herein, the term "opioid" refers to any agent that activates opioid receptors. Examples of opioids include endogenous opioid peptides, opium alkaloids (e.g. morphine), semi-synthetic opioids (e.g. heroin), and fully synthetic opioids (e.g. methadone).

Term "opioid withdrawal syndrome" refers to a syndrome characterized by signs and symptoms that appear when an opioid that causes physical dependence is regularly used for a long time and then suddenly discontinued or decreased in dosage. Such signs and symptoms may include, but are not limited to, sweating, malaise, anxiety, depression, persistent and intense penile erection in males (priapism), extra sensitivity of the genitals in females, general feeling of heaviness, cramp-like pains in the limbs, yawning and lacrimation, sleep difficulties, cold sweats, chills, severe muscle and bone aches not precipitated by any physical trauma, nausea and vomiting, diarrhea, goose bumps, cramps, fever, painful conditions, muscle spasms in the legs of the user (restless leg syndrome).
The term "antagonist" refers to a molecule that prevents the activation of a receptor.

Term "peripherally restricted antagonist of opioid receptors" refers to a molecule that prevents the activation of peripheral opioid receptors and does not prevent the activation of central opioid receptors. Nonexclusive examples of opioid receptors include μ (mu), κ (kappa), and δ (delta) opioid receptors.

Term "treating" refers to preventing opioid withdrawal syndrome from occurring in a subject that may be predisposed to the withdrawal syndrome due to regular use of opioids; and/or inhibiting or slowing opioid withdrawal syndrome, e.g. arresting its development.

In one embodiment of the invention, the peripherally restricted antagonist of an opioid receptor is a compound of formula (I):

\[
\begin{align*}
\text{CH}_3 & \quad R \\
\text{H} & \quad + \\
\text{N} & \quad X^- \\
\text{HO} & \quad (\text{I}) \\
\text{HO} & \quad \text{O} \\
\text{O} & \quad \text{CO}
\end{align*}
\]

wherein R is chosen from the cyclopropylmethyl and allyl, and X is a pharmaceutically acceptable anion.

As used herein, the term "pharmaceutically acceptable anion" means an anion substantially non-toxic and substantially non-deleterious to the mammal, preferably human. Preferably, the pharmaceutically acceptable anion is iodide. The respective compound of formula (I) can be prepared by methods well-
known from the art, for example, by the reaction of methyliodide with tertiary
morphinan, wherein the morphinan is naloxone or naltrexone.

Preferably, the compound of formula (I) is selected from the group consisting of 4,5alpha-Epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)morphinanum iodide and 17-(Cyclopropylmethyl)-4,5alpha-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanum iodide.

4,5alpha-Epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)morphinanum iodide is quaternary derivative of naloxone well known from the art, CAS Registry Number 73232-50-5. The synonyms are N-methylnaloxone and methylnaloxonium.

17-(Cyclopropylmethyl)-4,5alpha-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanum iodide is quaternary derivative of naltrexone well known from the art, CAS Registry Number 83387-25-1. The synonyms are N-methylnaltrexone and methylnaltrexonium.

Methylnaloxonium and methylnaltrexonium iodides can be prepared by methods well-known from the art, for example, by a reaction of methyliodide with naloxone and naltrexone respectively.

As used herein, the term "effective amount" means an amount of the peripherally restricted antagonist of an opioid receptor, the amount is useful for preventing, inhibiting or slowing opioid withdrawal syndrome, e.g. arresting its development. The particular dosage of the peripherally restricted antagonist of an opioid receptor required for treating opioid withdrawal syndrome according to this invention will depend upon the particular circumstances of the conditions to be treated. Considerations such as dosage, route of administration, and frequency of dosing are best decided by the attending physician. Preferably, the
effective amount of the peripherally restricted antagonist of an opioid receptor is from 0.001 mg per kg to 10 mg per kg body weight of the mammal.

Further, the present invention provides the use of a peripherally restricted antagonist of an opioid receptor for manufacturing a medicament for the treatment of opioid withdrawal syndrome. Preferably, the peripherally restricted antagonist of an opioid receptor is a compound of formula (I). More preferably, the compound of formula (I) is selected from the group consisting of 4,5\textalpha-Epoxy-3, 14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)morphinanum iodide and 17-(Cyclopropylmethyl)-4, 5\textalpha-epoxy-3, 14-dihydroxy-17-methyl-6-oxomorphinanum iodide.

In form of a medicament, the peripherally restricted antagonist of an opioid receptor can be administered by a route selected from a group consisting of oral, intranasal, sublingual, intramuscular, intravenous, subcutaneous, parenteral, or topical. Preferably, the peripherally restricted antagonist of an opioid receptor is administered parenterally.

The medicament of the invention can be prepared by known procedures using well-known ingredients. In making the medicaments, the active ingredients will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, tablet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The medicaments can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, sprays, soft and hard gelatin capsules, aerosols, suppositories, sterile injectable solutions, eye drops, eye gels, and sterile packaged powders.
Some examples of suitable carriers, diluents, and excipients include lactose, dextrose, sorbitol, mannitol, calcium phosphate, alginates, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, stearic acid, and mineral oil. The medicaments can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents.

Additionally, the peripherally restricted antagonists of an opioid receptor are well suited to formulation as sustained release dosage forms. The formulations can also be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. Such formulations would involve coatings, envelopes, or protective matrices which may be made from polymeric substances or waxes.

In accordance with the present invention, treating of withdrawal syndrome with the peripherally restricted antagonist of an opioid receptor can be a part of a complex therapy for treating opioid withdrawal syndrome. Accordingly, the peripherally restricted antagonist of an opioid receptor can be used in combination with antidepressants, neuroleptics, anxiolytics, and the like.

The following examples are presented to demonstrate the invention. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

Example 1

This example shows the efficacy of the peripherally restricted antagonist of opioid receptors for treating opioid withdrawal syndrome.

Wistar male rats were made morphine-dependent over 16 days with two daily (8 a.m. and 8 p.m.) i.p. injections of morphine in doses from 5 to 80
mg/kg, by increasing doses by 5 mg/kg per day. Thirty-six hours after the last injection the morphine-dependent rats received i.p. injections of saline (Control) or Methylnaloxonium iodide in dose of 2 mg per kg body weight (n=8 in each group). One hour later, different withdrawal signs were assessed including open field ambulation and rearing, the presence and recurrence of grooming, wet dog shakes, diarrhea, dyspnea, ptosis, piloerection, writhings, seizures, escape attempts, rhinorrea, paw shakes, head shakes, teeth chattering and posture disturbance. The total withdrawal score was calculated and used as a withdrawal index mean ± SD (n=8) for comparison of the severity of the withdrawal syndrome in morphine-dependent rats treated with Methylnaloxonium iodide or saline (Control). Data are presented in Table 1.

Table 1
Withdrawal Index in Morphine-Dependent Rats Treated with Methylnaloxonium Iodide.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Withdrawal Index, mean± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (saline)</td>
<td>6.17 ± 0.41</td>
</tr>
<tr>
<td>Methylnaloxonium iodide, 2 mg/kg</td>
<td>3.20 ± 0.13*</td>
</tr>
</tbody>
</table>

*Differs significantly from the Control (p<0.05).

The table shows significant decrease in withdrawal index in the morphine-dependent rats administered with 2 mg/kg of methylnaloxonium iodide as compared to the Control. Thus, methylnaloxonium iodide, the peripherally restricted antagonist of opioid receptors, is useful for the treatment of opioid withdrawal syndrome.

Example 2
This example shows medicaments comprising the peripherally restricted antagonist of opioid receptors for treating opioid withdrawal syndrome (Table 2 and 3).

Table 2

<table>
<thead>
<tr>
<th>Tablets</th>
<th>Per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of formula I</td>
<td>100 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>140 mg</td>
</tr>
<tr>
<td>Corn starch</td>
<td>240 mg</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>15 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

The compound of formula I, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

Table 3

<table>
<thead>
<tr>
<th>Ampoule solution</th>
<th>Per ampoule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of formula I</td>
<td>50 mg</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>50 mg</td>
</tr>
<tr>
<td>Water for injections</td>
<td>5 ml</td>
</tr>
</tbody>
</table>

The compound of formula I is dissolved in water at its own pH and sodium chloride is added to make it isotonic. The solution obtained is filtered
free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilized and sealed by fusion. The each ampoule contains 50 mg of active substance.
WE CLAIM:

1. A method for treating opioid withdrawal syndrome comprising administering to a mammal in need thereof an effective amount of a peripherally restricted antagonist of an opioid receptor.

2. The method of claim 1, wherein the peripherally restricted antagonist of an opioid receptor is a compound of formula (I):

```
CH3
N
R

X-
```

wherein

R is chosen from the cyclopropylmethyl and allyl, and

X is a pharmaceutically acceptable anion.

3. The method of claim 2, wherein said compound is selected from the group consisting of 4,5alpha-Epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)morphinanum iodide and 17-(Cyclopropylmethyl)-4,5alpha-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanum iodide.

4. The method of claim 1, wherein the effective amount of said antagonist is from 0.001 to 10 mg per kg body weight of a mammal.

5. The method of claim 1, wherein the mammal is a human.

7. The use of claim 6, wherein the peripherally restricted antagonist of an opioid receptor is a compound of formula (I):

![Chemical Structure](attachment:image)

wherein

R is chosen from the cyclopropylmethyl and allyl, and
X is a pharmaceutically acceptable anion.

8. The use of claim 7, wherein said compound is selected from the group consisting of 4,5α-Epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)morphinanum iodide and 17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanum iodide.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K3/485 A61P25/36 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 2004/005294 A (SCHMIDHAMMER HELMUT [AT]; SPETEA MARIANA [AT]; SCHUETZ JOHANNES [AT];) 15 January 2004 (2004-01-15) page 2, paragraphs 3,4 page 13, paragraph 2 - page 14, paragraph 1 claims 2,8</td>
<td>1,2,4-7</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C See patent family annex

* Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art
"S" document member of the same patent family

Date of the actual completion of the international search 14 November 2007
Date of mailing of the international search report 12/12/2007

Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

Authorized officer Collins, Sally
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>A. HAMLIN, K. M. BULLER, T. A. DAY, P.B. OSBORNE: &quot;Peripheral withdrawal recruits distinct central nuclei in morphine-dependent rats&quot; NEUROPHARMACOLOGY, vol. 41, 2001, pages 574-581, XP002456346 page 574, column 1, paragraph 1 - column 2, paragraph 1 page 575, column 2, paragraph 2 page 580, column 2, paragraph 2</td>
<td>1-8</td>
</tr>
</tbody>
</table>
### Patent Document Family

<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CA 2491689 A1</td>
<td>15-01-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1665819 A</td>
<td>07-09-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 10229842 A1</td>
<td>05-02-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1554282 A2</td>
<td>20-07-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2006500326 T</td>
<td>05-01-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2005182258 A1</td>
<td>18-08-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR PI0409133 A</td>
<td>02-05-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2521379 A1</td>
<td>28-10-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1767831 A</td>
<td>03-05-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1615646 A1</td>
<td>18-01-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2006522818 T</td>
<td>05-10-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA05010817 A</td>
<td>30-03-2006</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (April 2005)