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(54) Title: NEW SYNERGISTIC PREPARATIONS CONTAINING DEZOCINE AND A LOCAL ANAESTHETIC AND A NEW METHOD OF ALLEVIATION OF PAIN

(57) Abstract

A pharmaceutical preparation for spinal analgesia, which alleviates postoperative or chronic pain containing dezocine or a physiologically acceptable salt thereof together with a local anaesthetic, such as bupivacaine or a physiologically acceptable salt thereof, a method for obtaining said preparation and a method of obtaining analgesia by administering said preparation to a patient in the need of analgesia.

UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

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New synergistic preparations containing dezocine and a local anaesthetic and a new method of alleviation of pain.

Field of the Invention

The present invention is related to new synergistic pharmaceutical preparations, a method for their preparation and to a new method of alleviation of postoperative pain and pain related to pathophysiological changes in man, such as severe chronic pain, wherein the new pharmaceutical preparations are used.

Background of the Invention

The suffering from pain after operations, and that related to diseases as cancer and neurological diseases, has been the subject to treatment with e.g. conventional opiate analgesics. These have several severe draw-backs, as e.g. development of tolerance, addiction and sedation with risk for respiratory depression. There is thus a need for analgesic agents intended for pain relief post-operatively and for relief of severe pain of other origins, which do not have the mentioned draw-backs. The opiate agonist/antagonist analgesics have been shown to have several advantages in this respect. Another type of drug that has been used spinally to treat pain, is the local anaesthetic compounds. Their disadvantage as analgesics is the undesired motor impairment that occurs at doses very close to those giving rise to analgesia. One possibility to avoid this is to combine an opiate agonistic/antagonistic drug with a local anaesthetic, in order to achieve an additive or synergistic analgesic effect thereof.

Prior art

The compound dezocine, (-)-13β-amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol, is described in e.g. US patent 4001331 and is known as an orally and parenterally active analgesic agent.

Outline of the Invention

According to the present invention it has been found that the known compound dezocine when administered together with a known local anaesthetic compound, e.g. bupivacaine, lidocaine, tetracaine or ropivacaine, gives an unexpected synergistic antinociceptive effect when administered intrathecally. The new preparations thus can be used to alleviate pain when administered intrathecally or epidurally.

Examples of physiologically acceptable salts, which are used according to this invention are hydrochloride, hydrobromide, lactate, acetate or sulphamate.

Especially preferred physiologically acceptable salts are the hydrochlorides of dezocine and bupivacaine.

The present invention thus provides new pharmaceutical preparations containing dezocine and a local anaesthetic agent, methods for preparing such preparations and methods for alleviating pain sensation wherein said pharmaceutical preparation is used in the post-operative period for the treatment of severe chronic pain. The pharmaceutical preparations are for spinal analgesia. They are preferably administered by intrathecal or epidural injection. In a preferred embodiment of this invention dezocine and

bupivacaine are incorporated in a pharmaceutical preparation suitable for intrathecal or epidural injection.

In a further preferred embodiment of this invention dezocine HCl is incorporated in a pharmaceutical preparation suitable for intrathecal injection together with bupivacaine HCl. A convenient route of administration of the new preparations is spinally i.e. intrathecally or epidurally, which will allow repeated administration over a long period of time. When administering the drug in this way intrathecally, a convenient way of restricting spread to segments more rostrally than intended, would be to make the solution hyperbaric by adding i.e. glucose to the desired density. To restrict the elimination of the drugs from the site of injection, a vasoconstrictor such as adrenaline may be added to the solution.

The dosage of administration of dezocine and the local anaesthetic depend i.a. on the route of administration and the pharmaceutical formulation. A suitable dosage for obtaining analgesia by intrathecal or epidural administration is between 3 and 500 µg/kg of dezocine and between 0.1 and 1.5 mg/kg of bupivacaine.

Pharmaceutical preparations

In clinical practice the preparations will normally be injected intrathecally or epidurally. The preparations used are solutions which contain between 0.01 and 0.1 % by weight of dezocine between 0.1 and 1 % by weight of the local anaesthetic, and between 5-10 % by weight of glucose in order to increase the baricity of the solution. It is also possible to add a small amount of the vasoconstrictor adrenaline to the solution in order to restrict spreading. The preparations are made by dissolving the active

ingredient or ingredients in a physiologically acceptable solvent.

Example 1

Dezocine HCl	0.6 mg/ml
Bupivacaine HCl	5 mg/ml
Sodium chloride	9 mg/ml
Distilled water	ad 100 ml

Example 2

Dezocine HCl	0.6 mg/ml
Bupivacaine HCl	5 mg/ml
Glucose	75 mg/ml
Sodium chloride	9 mg/ml
Distilled water	ad 100 ml

Example 3

Dezocine HCl	0.6 mg/ml
Bupivacaine HCl	5 mg/ml
Adrenaline	12.5 µg/ml
Sodium chloride	9 mg/ml
Distilled water	ad 100 ml

Example 4

Dezocine HCl	0.6 mg/ml
Lidocaine HCl	50 mg/ml
Sodium chloride	9 mg/ml
Distilled water	ad 100 ml

Example 5

Dezocine HCl	0.6 mg/ml
Ropivacaine HCl monohydrate	7.5 mg/ml
Sodium chloride	9 mg/ml
Distilled water	ad 100 ml

Example 1 is considered to represent the best mode of carrying out the invention known at present.

Pharmacological tests

The antinociceptive effect of the new preparations may be established by the hot plate and tail-flick test.

Testing of tail-flick was performed using an IITC inc. Mod. 33 Analgesiameter^{R}, with the light focused on the tip of the tail (d'Amour, F.E and Smith, D.L. J. Pharmacol. Exp. Ther. 72, 74, 1941). The intensity of the beam was adjusted to give a reaction time of 3-4 sec. before intrathecal injection of the drug solutions. For the hot plate testing, a modification of the Eddy and Leimbach method (Eddy, N.B. and Leimbach, D.J. Pharmacol. Exp. Ther. 107, 385, 1952) was used. An IITC Inc. Mod. 35-D Analgesiameter^{R} was set at a temperature of 58±0.2°C. The criteria for a pain response was licking or kicking of either of the hindpaws. The cut-off time in the hot plate test was 30 sec. and in the tail-flick test 10 sec.

The pain responsiveness was examined in male NMRI mice in a weight range of 22-25 g. They were housed in groups of 10 in each cage for at least 4 days after delivery.

All drugs were administered by the lumbar puncture technique, essentially as that originally described by Hylden and Wilcox, Eur. J. Pharmacol. 67, 313, 1980. In brief, a 30 G stainless steel cannula was inserted through

the lumbar L4/L5 vertebral interspace, and the drug solution was delivered with a microsyringe, attached to the cannula by a PE 50 polyethylene tube. The drugs were delivered in a volume of 5 µl.

After the injections, the animals were tested for hot plate and tail-flick tests. The drugs were administered in a volume of 5 µl, and testing of hot plate and tail-flick reaction latencies took place at the intervals given in the tables. The animals were not tested until the local anaesthetic effect of bupivacaine had disappeared, which normally took between 10 and 15 minutes.

In the experiments with combinations of dezocine HCl and bupivacaine HCl, the results illustrate that the substances act in a synergistic way, c.f. Tables 1A and 1B. Although the effect of 3 µg dezocine, and also that of bupivacaine alone, completely had disappeared 2 hours after injection, a strong antinociceptive effect could be found for the new combination. In this study, the statistical difference was calculated for dezocine compared to dezocine injected together with bupivacaine. In the hot plate test, c.f. Table 1B, some additive effect might have occured at 30 min after injection, since the animals injected with bupivacaine alone had a slight antinociceptive effect at this time. It is however obvious, from the Tables 1A and 1B, that the contribution of dezocine to the antinociceptive effect of the preparation is more than additive. Regarding the local anesthesia, this appeared to be the same regardless whether bupivacaine HCl was injected alone or together with dezocine HCl. The duration of the motor blockade was thus between 15 and 20 min regardless of whether bupivacaine was injected alone or together with dezocine.

Table 1A and 1B

Antinociceptive effects of dezocine HCl at a dose of 3 µg alone or combined with 37.5 µg bupivacaine HCl in the tail-flick (A) or hot plate (B) tests. The cut-off time in the tail-flick test was 10 sec and in the hot plate test 30 sec. The values are reaction times (seconds) expressed as means ± S.E.M. and represent the results from experiments performed in 10 mice. Note that the reaction time at 0 min represents the basal value for the animals, and that an increase from this value represents antinociception. The synergistic antinociceptive effects in animals injected with the combination of dezocine and bupivacaine is therefore, obvious at 60 and 120 min. in the tail-flick test and at 30 and 60 min. in the hot plate test (Mann-Whitney U-test). ** $P<0.01$ when the difference between dezocine injected alone or together with bupivacaine is calculated.

Table 1A

Intrathecal administration of dezocine and/or bupivacaine
tail-flick test, mouse

Minutes	Dezocine 3 µg	Bupivacaine 37.5 µg	Dezo+Bupi 3 µg + 37.5 µg
0	4.7 ± 0.1	4.6 ± 0.1	4.8 ± 0.1
30	10.0 ± 0.0	8.3 ± 0.6	10.0 ± 0.0
60	8.2 ± 0.4	5.1 ± 0.2	10.0 ± 0.0 **
120	5.2 ± 0.2	4.6 ± 0.1	8.5 ± 0.4 **
180	4.9 ± 0.2	4.5 ± 0.1	5.0 ± 0.2

Table 1B

Intrathecal administration of dezocine and/or bupivacaine
hot plate test, mouse

Minutes	Dezocine 3 µg	Bupivacaine 37.5 µg	Dezo+Bupi 3 µg + 37.5 µg
0	5.2 ± 0.5	5.3 ± 0.3	5.1 ± 0.4
30	12.8 ± 1.2	9.8 ± 1.1	23.1 ± 1.7 **
60	8.0 ± 0.9	7.8 ± 0.7	14.9 ± 1.7 **
120	5.2 ± 0.6	6.5 ± 0.7	7.6 ± 1.5
180	5.3 ± 0.6	5.0 ± 0.5	5.8 ± 0.4

Claims

1. A pharmaceutical preparation for spinal analgesia, characterized in that it contains dezocine or a physiologically acceptable salt thereof together with a local anaestetic agent or a physiologically acceptable salt thereof.

2. A pharmaceutical preparation according to claim 1 characterized in that it also contains glucose.

3. A pharmaceutical preparation according to claim 1 characterized in that it also contains adrenaline.

4. A pharmaceutical preparation according to claim 1 characterized in that it contains dezocine in an amount of between 0.01 and 0.1 % by weight and the local anaesthetic agent in an amount of between 0.1 and 1 % by weight.

5. A pharmaceutical preparation according to claims 1-4 characterized in that the local anaesthetic agent is bupivacaine or a physiologically acceptable salt thereof.

6. A pharmaceutical preparation according to claims 2 and 5 characterized in that it contains 0.06 % by weight of dezocine, 0.5 % by weight of bupivacaine and 5-10 % by weight of glucose.

7. A pharmaceutical preparation according to claim 1 characterized in that it contains 0.06 % by weight of dezocine and 1 % by weight of ropivacaine.

8. A method for the preparation of a pharmaceutical preparation according to claim 1 characterized in dissolving dezocine or a physiologically acceptable

salt thereof together with a local anaesthetic agent or a physiologically acceptable salt thereof in a pharmaceutically acceptable solvent.

9. A method of obtaining analgesia comprising intrathecal or epidural injection to a patient in the need of analgesia an amount of dezocine or a physiologically acceptable salt thereof effective to obtain analgesia together with an amount of a local anaesthetic or a physiologically acceptable salt thereof effective to obtain local anaesthesia.

10. Use of dezocine together with a local anaesthetic in the manufacture of a pharmaceutical preparation with analgesic effect.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE89/00348

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A61K 31/135, 31/445, 45/06

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y,A	EP,A1, 0 164 320 (ASTRA LÄKEMEDEL AKTIEBOLAG) 11 December 1985, see inter alia page 2, line 7 - page 3, line 7 & GB, 2155336 JP, 60226809	1 - 8, 10
Y	EP,A1, 0 180 303 (AMERICAN HOME PRODUCTS CORPORATION) 7 May 1986, see especially page 2, first paragraph & GB, 2165149 JP, 61085314 US, 4605671 AU, 572689	1 - 8, 10
A	US,A, 2 382 546 (D. CURTIS) 14 August 1945, see especially page 8, left column, lines 22-38	1 - 8, 10

.../...

[10] 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

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"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.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1989-09-13	1989 -09- 15
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Martin Hjälmdahl Martin Hjälmdahl

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 9, because ~~they~~ it relate~~s~~ to subject matter not required to be searched by this Authority, namely:

Method for treatment of the human or animal body by therapy /PCT Rule 39 (iv)/

2. [X] Claim numbers 1-4, 8 and 10, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The expressions "a local anaesthetic agent" and "a local anaesthetic" are too broad and lack differentiating power. The search on said claims has therefore been incomplete.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	Anesthesia and Analgesia, Volume 62, No. 10 issued 1983 (New York), J.C. Rowlingson et al, "Anesthetic potency of dezocine and its interaction with morphine in rats", see pages 899-902, especially p. 900, right column, second paragraph.	1 - 8, 10
Y	Anesthesia and Analgesia, Volume 57, issued 1978 (Cleveland), R.J. Fragen & N. Caldwell, "Comparison of dezocine (WY 16, 225) and meperidine as post-operative analgesics", see pages 563-566, especially p. 563, first paragraph.	1 - 8, 10