Treatment of dementia and neurodegenerative diseases with intermediate doses of LHRH antagonists

The present invention relates to the treatment of dementia and neurodegenerative diseases with intermediate doses of LHRH antagonists which do not cause a castration.

FURUYA, Shuichi et al. in WO 01/78780 teach preventives and remedies for Alzheimer's disesase containing a compound having GnRH antagonism have effects of preventing and treating Alzheimer's disease with little toxicity.

It has been shown in a study by Bowen R.L et al. that serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were significantly higher in individuals suffering of dementia , e.g. Alzheimer's disease. Bowen R.L. et al. propose in their patent application CA 2,309,395 (US priority June 4, 1999, 09/326,180) to lower FSH and LH to minimal levels by the use of castrating doses of analogues of the LH-releasing hormone (LHRH), either super-agonists or antagonists.
This treatment would be accompanied by highly undesirable side effects as lowering sex hormone levels to castration levels would result in loss or reduction of libido, sexual desire and sexual potency. In men and pre-menopausal women this treatment would also result in the typical symptoms of drop of sex hormones like hot flushes, etc. Women would additionally suffer from loss of bone minerals that would limit the treatment.
These side effects could be reduced by hormone replacement therapy.

It has been found now that the treatment with intermediate doses of LHRH antagonists results in a sub-maximal lowering of FSH and LH to normal levels that leaves sex hormone levels above the castration treshold.
This treatment is highly advantageous as it gives the desired results of normalising FSH and LH levels without the undesirable side-effects of sex hormone blockade. Thus the additional treatment of sex hormone replacement becomes superfluous.

Accordingly, an aspect of the present invention provides a use of a LHRH antagonist for the preparation of a medicament for the treatment of dementia and neurodegenerative diseases in humans by administration of intermediate doses, which do not cause a lowering of sex hormone levels to castration levels, wherein the LHRH antagonist is cetrorelix, teverelix, antide, abarelix, D-63 153 (Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2) or peptidomimetic.

An embodiment of the present invention may relate to the treatment of dementia and neurodegenerative diseases with intermediate doses of LHRH antagonists, wherein the antagonist is cetrorelix, teverelix, antide or abarelix. The antagonist can also be the LHRH antagonist D-63 153 (Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2) as described in the PCT application WO 00/55190 A1.

The mentioned LHRH antagonists can also exhibit a heterocyclic skeletal structure. Such peptidomimetics can be for example

- 1-[7-Chloro-3-(3,5-dimethyl-phenyl)-2-oxo-4-(2-piperidin-2-yl-ethoxy)-1,2-dihydro-quinolin-6-yl]-3-pyridin-2-yl-urea (described in WO 97/44339),
- 3-[Benzyl-methyl-amino)-methyl]-2-*tert*-butyl-8-(2-fluoro-benzyl)-6-(3-methoxy-phenyl)-7-methyl-8*H*-imidazo[1,2-a]pyrimidin-5-one (described in WO 01/29044),
- 2-(2,5-Dimethyl-furan-3-yl)-8-(2-fluoro-benzyl)-3-([methyl-(2-pyridin-2-yl-ethyl)-amino]-methyl)-5-oxo-5,8-dihydro-imidazo[1,2-a]pyrimidine-6-carboxylic acid 1-ethyl-propylester (described in WO 00/69859),
- 3-((2-[2-(3,5-Difluoro-phenyl)-1-(2-methoxy-benzoyl)-2-oxo-ethylidene]-2,3-dihydro-1*H*-benzoimidazol-5-yl-amino)-methyl)-benzonitrile (described in WO 02/02533).

The LHRH antagonist is given in a monthly dose of 10 to 100 mg per month and the treatment is repeated monthly, two-monthly or lasting several months.

In a preferred embodiment the LHRH antagonist is given in a monthly dose of 30 to 60 mg per month and the treatment is repeated monthly, two-monthly or lasting several months.

Pharmaceutical formulations of the LHRH antagonist suitable for the therapeutic management of dementia and neurodegenerative diseases may be for example

a) acetate salt formulations of the active compounds in the concentration of 1 mg/1 ml or lower where the lyophilisate powder may be dissolved in water for injection or in gluconic acid;

b) acetate salt formulations of the active compounds in the concentration of 1.5 mg/1 ml to 5.0 mg/1 ml, prèferably 2.5 mg/1 ml where the lyophilisate powder may be dissolved in water for injection or in gluconic acid;

c) pamoate salt formulations of the active compounds in the concentration of 10 mg/1 ml to 30 mg/1 ml, preferably 15 mg/1 ml where the lyophilisate powder may be dissolved in gluconic acid or in water for injection.

Suitable excipients and dosage forms are for example described by K.H. Bauer, K.-H. Frömming and C. Führer, Lehrbuch der Pharmazeutischen Technologie, 6th edition, Stuttgart 1999, pages 163-186 (excipients) and pages 227-386 (dosage forms), including the references as cited therein.

The LHRH antagonist can be administered for example subcutaneous, oral, intramuscular or inhalative.

The disease as mentioned, for example can be treated in accordance with the following scheme.

Example

In one embodiment of the invention a single dose of 30-60 mg of cetrorelix is administered by injection per month. The treatment is continued monthly.
In another embodiment the treatment is continued two-mothly or lasting several months after the administration of the single dose.

Claims

1. Use of a LHRH antagonist for the preparation of a medicament for the treatment of dementia and neurodegenerative diseases in humans by administration of intermediate doses, which do not cause a lowering of sex hormone levels to castration levels, wherein the LHRH antagonist is cetrorelilx, teverelix, antide, abarelix, D-63 153 (Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2) or a peptidomimetic.

2. Use according to claim 1, characterized in that the monthly single dose is in the range of 10-100 mg LHRH antagonist.

3. Use according to claims 1 and 2, characterized in that the monthly single dose is about 30 to about 60 mg LHRH antagonist.

4. Use according to one of claims 1 to 3, characterized in that the administration is continued on a monthly or two-monthly or lasting several months base.

5. Use according to one of claims 1 to 4, characterized in that the treated disease is Alzheimer's disease.

6. Use according to any of claims 1 to 5 in which the peptidomimetic is a compound

- 1- [7-Chloro-3- (3, 5-dimethyl-phenyl)-2-oxo-4-(2-piperidin-2-yl-ethoxy)-1,2-dihydro-quinolin-6-yl]-3-pyridin-2-yl-urea
- 3-[Benzyl-methyl-amino)-methyl]-2-*tert*-butyl-8-(2-fluoro-benzyl)-6-(3-methoxy-phenyl)-7-methyl-8*H*-imidazo[1,2-a]pyrimidin-5-one
- 2-(2,5-Dimethyl-furan-3-yl)-8-(2-fluoro-benzyl)-3-([methyl-(2-pyridin-2-yl-ethyl)-amino]-methyl)-5-oxo-5,8-dihydro-imidazo[1,2-a]pyrimidine-6-carboxylic acid 1-ethyl-propylester or
- 3-((2-[2-(3,5-Difluoro-phenyl)-1-(2-methoxy-benzoyl)-2-oxo-ethylidene]-2,3-dihydro-1*H*-benzoimidazol-5-yl-amino)-methyl)-benzonitrile.