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(54) Title: TREATMENT OF DEMENTIA AND NEURODEGENERATIVE DISEASES WITH INTERMEDIATE DOSES OF LHRH ANTAGONISTS

(57) Abstract: The present invention relates to the treatment of dementia and neurodegenerative diseases like Alzheimer's disease with intermediate doses of LHRH antagonists which do not cause a castration. A preferred LHRH antagonist is cetrorelix.

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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 disease 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 now 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 threshold.

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.

According to a first aspect of the present invention, there is provided the 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 castration, wherein a monthly single dose is in the range of 10 – 100 mg LHRH antagonist.

According to a second aspect of the present invention, there is provided a method for the treatment of dementia or neurodegenerative diseases in humans, which method comprises administering intermediate doses of a LHRH antagonist which do not cause a

castration, wherein a monthly single dose is in the range of 10 – 100 mg LHRH antagonist.

According to a third aspect of the present invention, there is provided a LHRH antagonist when used for the treatment of dementia or neurodegenerative diseases in humans by administration of intermediate doses which do not cause a castration, wherein a monthly single dose is in the range of 10 to 100 mg LHRH antagonist.

The present invention relates to the treatment of dementia and neurodegenerative diseases with intermediate doses of LHRH antagonists, wherein the antagonist is preferably 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

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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, preferably 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 1

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-monthly or lasting several months after the administration of the single dose.

Example 2

Reference is made to Tables 1 and 2:

Table 1: Recorded average testosterone levels of male test persons aged 50+ years during treatments with different single monthly doses of Cetrorelix (30 mg, 60 mg, 90 mg) over a period of 4 weeks

Table 1

week	Testosterone [ng/mL]		
	30 mg CET	60 mg CET	90 mg CET
0	8.9	7.2	7.2
1	6.5	2.7	1.2
2	7.2	5.2	3.0
3	7.4	6.4	3.1
4	8.2	8.8	6.0

Table 2: Recorded median LH levels of female test persons during treatment with a single monthly dose of 60 mg Cetrorelix over a period of 4 weeks following an initial treatment cycle with Cetrorelix

Table 2

week	LH [U/L]
	60 mg CET
0	5.3
1	5.0
2	4.7
3	3.5
4	5.7

Table 1 demonstrates the effectiveness of a treatment according to the present invention. Testosterone levels that are a direct measure of LH/FSH serum levels are successfully reduced by administration of intermediate doses of Cetrorelix in a dose-dependent fashion without causing a hormonal castration.

Within the dose range tested (30 mg, 60 mg, 90 mg Cetrorelix) all doses show an advantageous non-castrating hormone reduction that decreases with decreasing amounts of GnRH antagonist administered. On the basis of these experimental data it is evident that doses much lower than 30 mg or much higher than 90 mg GnRH antagonist per month will not affect the therapeutic benefits as described.

Analogously, Table 2 shows the beneficial effects of a monthly single dose of 60 mg Cetrorelix on LH serum levels in female test persons. These women were treated in

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the course of two treatment cycles, i.e. including a preceding initial 4 weeks Cetrorelix treatment. The LH profile presented is represented for the profile to be expected in the course of a long-term repetitive treatment. Again, no castration levels [(almost) complete LH elimination from the blood] were reached.

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The claims defining the invention are as follows:

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 castration, wherein a monthly single dose is in the range of 10 – 100 mg LHRH antagonist.

2. Use according to claim 1, wherein a monthly single dose is in the range of 30 – 100 mg LHRH antagonist.

3. Use according to claim 1 or 2, wherein a monthly single dose is about 30 to about 60 mg LHRH antagonist.

4. Use according to any one of claims 1 to 3, wherein a monthly single dose is in the range of 60 – 100 mg LHRH antagonist.

5. Use according to any one of claims 1 to 4, wherein a treatment is repeated monthly, two-monthly or lasting several months.

6. Use according to any one of claims 1 to 5, wherein a treated disease is Alzheimer's disease.

7. Use according to one of claims 1 to 6, 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 a peptidomimetic.

8. Use according to claim 7 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-8H-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-1H-benzoimidazol-5-yl-amino)-methyl)-benzonitrile.

9. A method for the treatment of dementia or neurodegenerative diseases in humans, which method comprises administering intermediate doses of a LHRH antagonist which do not cause a castration, wherein a monthly single dose is in the range of 10 – 100 mg LHRH antagonist.

10. A method according to claim 8 or 9, wherein a monthly single dose is in the range of 30 – 100 mg LHRH antagonist.

11. A method according to any one of claims 8 to 10, wherein a monthly single dose is about 30 to about 60 mg LHRH antagonist.

12. A method of any one of claims 8 to 11, wherein a monthly single dose is in the range of 60 – 100 mg LHRH antagonist.

13. A method according to any one of claims 8 to 12, wherein the treatment is repeated monthly, two-monthly or lasting several months.

14. A method of any one of claims 8 to 13, wherein the treated disease is Alzheimer's disease.

15. A method according to any one of claims 8 to 14, 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 a peptidomimetic.

16. A method according to claim 15 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-8H-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-1H-benzoimidazol-5-yl-amino)-methyl)-benzonitrile.

17. An LHRH antagonist when used for the treatment of dementia or neurodegenerative diseases in humans by administration of intermediate doses which do not cause a castration, wherein a monthly single dose is in the range of 10 to 100 mg LHRH antagonist.

18. Use as claimed in claim 1, said use substantially as hereinbefore described with reference to the Example 1.

19. A method as claimed in claim 8, said method substantially as hereinbefore described with reference to the Example 1.

20. A LHRH antagonist when used for the treatment of dementia or neurodegenerative diseases in humans by administration of intermediate doses which do not cause a castration, substantially as hereinbefore described with reference to Example 1.

Dated 28 February, 2007
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