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(54) **METHOD FOR IMPROVING DISTURBANCIES OF ACTIVITIES OF DAILY LIVING AFTER STROKE**

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(57) **ABSTRACT**

There is described a method for improving the disturbancies of Activities of the Daily Living in post-stroke patients by early administration of nefiracetam after the stroke. This method of treatment allows an improvement in the recovery from stroke.

METHOD FOR IMPROVING DISTURBANCIES OF ACTIVITIES OF DAILY LIVING AFTER STROKE

FIELD OF THE INVENTION

[0001] The present invention concerns the use of a cyclic gamma-aminobutyric acid (GABA) derivative, namely N-(2,6-dimethylphenyl)-2-(2-oxo-1-pyrrolidinyl)acetamide, as a drug for improving disturbances of the Activities of Daily Living (ADL) after a stroke or for recovering, or at least for improving the recovery of, a post-stroke patient.

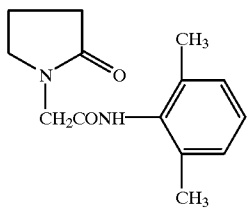
BACKGROUND OF THE INVENTION

[0002] Cyclic GABA derivatives, more particularly 2-oxopyrrolidine derivatives, are compounds extensively used in pharmaceutical compositions for the improvement of memory and attention and are known as mnemotonic or nootropic agents. Typical drugs of this class include 2-oxo-1-pyrrolidineacetamide (piracetam), 1-(4-methoxybenzoyl)-2-pyrrolidinone (aniracetam) and 4-hydroxy-2-oxo-1-pyrrolidineacetamide (oxiracetam).

DESCRIPTION OF THE PRIOR ART

[0003] It is known (BE 883791 - U.S. Pat. No. 4,341,790) that anilides of 2-oxo-1-pyrrolidineacetamide show central vasoactive and tranquillizing properties as well as the ability of regulating the metabolism and inhibiting thrombocyte agglutination. Thus, said compounds are deemed to be useful for the treatment of cerebro-ischaemic or atrophic diseases, brain irrigation disorders, brain atrophic crises as well as of brain aging processes. Among these anilides of 2-oxo-1-pyrrolidineacetamide, the 2,6-dimethylanilide, i.e. N-(2,6-dimethylphenyl)-2-(2-oxo-1-pyrrolidinyl)acetamide, known and hereinafter refferd to as nefiracetam, represented by the formula (A)

(A)



[0004] has been reported to be effective in prolonging the survival time upon a decrease in blood oxygen level and in relieving failure of memory due to cerebropathy.

[0005] The literature extensively discloses (see for example E. Ohtomo et al., J Clin. Exp. Med., Suppl., 1994, 170/9, 777-816) the usefulness of nefiracetam in improving psychiatric disorders associated with cerebrovascular diseases such as stroke (cerebral infarction or cerebral hemorrhage), this activity being a consequence of the favorable action of nefiracetam on the cerebral irrigation, as suggested by BE 883791.

[0006] It is also known (K. Hirata et al., Brain Topography 1996, 8/3, 279-284) that nefiracetam acts as a cerebral metabolic enhancer in improving the mental function impairment in stroke patients, thus confirming the suggestion of BE 833791 which disclosed the metabolism-regulating properties of the compound.

[0007] Moreover, it is known (U.S. Pat. No. 5,886,023) that nefiracetam improves symptoms of cerebrovascular or Alzheimer's type dementia due to a decline in mental function.

[0008] All these documents indicate that the efficacy of nefiracetam in the symptomatic treatment of impaired mental function is due to its ability in improving the cerebral irrigation or to its metabolism-regulating properties. Psychiatric symptoms and cognitive impairment are frequently observed following stroke and negatively affect both the patient and the caregiver.

[0009] In the above-cited article of Ohtomo et al., the global results of a clinical study, conducted in two groups of patients to which nefiracetam and, respectively, placebo were administered after a stroke (celebral infarction or celebral hemorrhage), showed that the compound improves the psychiatric symptoms but concluded that there was no significant difference between the two groups as far as the activities of daily living were concerned. Thus, according to these results nefiracetam appeared as inactive in improving the disturbances of the activities of daily living in post-stroke patients.

[0010] On the other hand, no drug is known for a positive effect in this indication. Such an effect could suggest a curative use of a drug for the recovery from a stroke or, at least, for an improved recovery from stroke.

SUMMARY OF THE INVENTION

[0011] It has now surprisingly been found that, if nefiracetam is administered to a patient, suffering from the consequences of a stroke, early after the event or at least within the first six months after the stroke, a significant improvement with regard to the global disturbances of the activities of the daily living is obseved.

[0012] More particularly, it has been found that nefiracetam is able to induce an improvement in the recovery of post-stroke patients, provided that said nefiracetam is administered early after the event at the most within the first six months after said event.

DETAILED DESCRIPTION OF THE INVENTION

[0013] Thus, it is an object of the present invention to provide a method for improving the disturbances of the Activities of Daily Living (ADL) in a post-stroke patient which comprises administering to said patient an effective dose of nefiracetam, said administration being initiated within the first six months after the event.

[0014] In order to display the best activity, nefiracetam will be administered early or at least as soon as possible, advantageusly within three month, preferably within one month after the stroke.

[0015] Nefiracetam can be administered in various manner to achieve the desired effect. The compound can be administered alone or in the form of pharmaceutical preparations to the patient to be treated, preferably orally. The oral amount of nefiracetam administered will vary and can be any effective amount according to the physician's prescrip-

tion. Normally, depending upon the patient and the mode of administration, the quantity of compound administered orally may vary over a wide range to provide from about 1 mg/kg to about 20 mg/kg, usually 1.5 mg/kg to 15 mg/kg of body weight of the patient per dose. Unit doses of nefiracetam can contain, for example, from about 50 mg to about 1200 mg, usually from 100 to 600 mg of the compound and may be administerd orally 1 to 4 times daily.

[0016] The activity of nefiracetam to improve the disturbancies of ADL has been discovered during a controlled clinical trial against placebo. The compound has been administered orally (450 mg/day) to 32 post-stroke patients within six months after the event whilst, concurrently, 27 patients received placebo. The two groups of patients were followed during at least 8 weeks and followed up at the end of week 4 and at the end of week 8 on a symptom scale measuring Activities of Daily Living. The nefiracetam-treated patients showed a moderate or remarkable improvement, whereas no patient in the group treated with placebo showed an improvement. Among the above 59 patients, 19 received nefiracetam and 10 received placebo within three months after stroke. Some 70% of the nefiracetam-treated patients showed a moderate or remarkable improvement whilst no improvement has be noted in the patients who received placebo. The difference was significant ($p=0.035$, χ^2 test). Thus, unlike what the literature seemed to suggest, it has been discovered that nefiracetam has the surprising and unique property of showing a dramatically good activity when given early after stroke. According to the results of this study, the early treatment with nefiracetam after stroke objectively improves the recovery from stroke, as shown by the fact that, beside psychiatric symptoms such as emotional disturbance and reduced spontaneity, also intellectual dysfunction dramatically improved in a high percent of nefiracetam-treated patients whilst no improvement was noted in the placebo-treated patients. Moreover, nefiracetam surprisingly tends to improve neurological signs and incontinence of urines. Thus nefiracetam, when administered early after the event, appears to be the first drug which is able to induce a recovery from stroke or, at least, to improve the recovery from stroke.

[0017] The mechanism of action of nefiracetam for this indication, which is not bound to the nootropic activity of the drug, is unknown, but it is believed that its surprising effect in improving the disturbancies of ADL after a stroke or in the recovery of, or at least in improving the recovery of, a post-stroke patient, is due to a true brain repair.

[0018] Thus, it is a second object of the present invention to provide a method for recovering, or at least for improving the recovery of, a post-stroke patient which comprises administering to said patient an effective amount of nefiracetam, said administration being initiated within three months from the stroke.

[0019] It is a third object of the present invention to provide a pharmaceutiacal composition for the improvement of the disturbancies of ADL in post-stroke patients comprising, as active ingredient, an effective amount of nefiracetam.

[0020] It is a fourth object of the present invention to provide a pharmaceutical composition for the recovery of, or at least for improving the recovery of, a post-stroke patient, comprising, as active ingredient, an effective amount of nefiracetam.

[0021] It is a fifth object of the present invention to provide the use of nefiracetam for the preparation of a medicament for improving the disturbancies of ADL in a post-stroke patient.

[0022] It is a sixth object of the present invention to provide the use of nefiracetam for the preparation of a medicament for the recovery, or at least for improving the recovery, of a post-stroke patient.

[0023] It is a seventh object of the present invention to provide the use of nefiracetam for the preparation of a medicament for the early treatment of stroke.

[0024] The pharmaceutical formulations in which form nefiracetam will normally be utilized, are prepared in a manner well known per se in the pharmaceutical art and usually comprise nefiracetam in admixture or otherwise in association with a pharmaceutically acceptable carrier or diluent thereof. For making those formulations the active ingredient will usually be mixed with a carrier, or diluted with a diluent, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other suitable container. Suitable carriers and diluents are known per se.

[0025] The formulations may be administered to the post-stroke patient for example in the form of tablets, capsules, dragees, suppositories, syrups or suspensions.

What is claimed is:

1. A method for improving the disturbances of the Activities of Daily Living (ADL) in a post-stroke patients which comprises administering to said patient an effective amount of nefiracetam, said administration being initiated within the first six months after the event.

2. A method according to claim 1 in which said administration is initiated within three months after said event.

3. A method for recovering, or at least for improving the recovery of, a post-stroke patient which comprises administering to said patient an effective amount of nefiracetam, said administration being initiated within six months from the stroke.

4. A method according to claim 3 in which said administration is initiated within three months from the stroke.

5. Pharmaceutiacal composition for the improvement of the disturbancies of ADL in a post-stroke patient comprising nefiracetam as active ingredient.

6. Pharmaceutical composition for the recovery of, or at least for improving the recovery of, a post-stroke patient, comprising nefiracetam as active ingredient.

7. Use of nefiracetam for the preparation of a medicament for improving the disturbancies of ADL in a post-stroke patient.

8. Use of nefiracetam for the preparation of a medicament for the recovery, or at least for improving the recovery, of a post-stroke patient.

9. Use of nefiracetam for the preparation of a medicament for the early treatment of stroke.

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