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(54) Titre : UTILISATION DE ROTIGOTINE POUR TRAITER OU PREVENIR LA PERTE DES NEURONES DOPAMINERGIQUES
(54) Title: USE OF ROTIGOTINE FOR THE TREATMENT OR PREVENTION OF DOPAMINERGIC NEURONE LOSS

(57) Abrégé/Abstract:
The invention relates to the use of rotigotine or salts thereof and prodrugs for the production of a medicament for the treatment or prevention of dopaminergic cell destruction in diseases which are connected to increased dopaminergic cell destruction. The invention also relates to the use of rotigotine as a medicament for the preventive treatment of Parkinson’s disease.
ABSTRACT

The invention relates to the use of rotigotine or salts thereof and prodrugs for the production of a medicament for the treatment or prevention of dopaminergic cell destruction in diseases which are connected to increased dopaminergic cell destruction. The invention also relates to the use of rotigotine as a medicament for the preventive treatment of Parkinson's disease.
Use of Rotigotine for the Treatment or Prevention of Dopaminergic Neurone Loss

Introduction

Parkinson’s disease occurs as a result of a chronic, progressive degeneration of neurones, the cause of which has not yet been completely clarified. It is clinically manifested in the form of the cardinal symptoms of resting tremors, rigidity, bradykinesia and postural instability.

Primarily used as medicaments for alleviating the motor symptoms are levodopa, dopamine agonists such as, for example, rotigotine, pramipexole, bromocriptine, ropinirole, cabergoline, pergolide, apomorphine and lisuride, anticholinergic agents, NMDA antagonists, β-blockers as well as the MAO-B inhibitor selegeline and the COMT inhibitor entacapone. Most of these active substances intervene in the dopaminergic and/or cholinergic signal cascade and symptomatically influence in this manner the motor disturbances that are typical of Parkinson’s disease.

The therapy of Parkinson’s disease has, to date, been initiated with the onset of the cardinal symptoms. Morbus Parkinson is generally deemed to be clinically confirmed if at least two of the four cardinal symptoms (bradykinesia, resting tremors, rigidity and postural instability) can be determined and L-Dopa has an effect (Hughes, J Neurol Neurosurg Psychiatry 55, 1992, 181). Unfortunately, however, patients with Parkinson’s disease only develop the motor disturbances once approximately 70 to 80% of the dopaminergic neurones in the substantia nigra (SN) have been irreversibly damaged (Becker et al, J Neurol 249, 2002, Suppl 3: III, 40; Hornykiewicz, Encyclopaedia of Life Science 2001, 1). The chances of a therapy with lasting effects are minimal at this time. It is thus desirable to commence therapy as early as possible.

Current clinical observations as well as anatomical and genetic research now show that it is possible to both diagnose patients with Parkinson’s disease at an early stage and to also identify high-risk patients.

The following, for example, can thereby be used as diagnostic markers:

- Biochemical markers, such as neuromelanin (Gerlach, Neurotox Res 5, 2003, 35; WO 02/31499), S-100 beta (Muramatsu, Glia 42, 2003, 307), alpha synuclein (WO 03/069332; WO 00/02053) or parkin protein (Sharma, Neurol Clin N Am 20, 2002, 759) and semaphorin (WO 03/007803).
- Genetic markers, such as the park genes 1-8 (Guttmann, CMAJ 4, 2003, 168; WO 03/766588); CYP2D6-B (WO 03/012137), chromosome 2q 36-37 (Pankratz, Am J Hum Gen 72, 2003, e-pub), a-synuclein (Polymeropoulos, Science. 276, 1997, 2045) or mutations in CYP2D6-B and GSTM1 deletion (WO 03/012137).
- Imaging methods, such as ultrasound examination of the SN size, possibly in combination with other methods (Becker et al, J Neurol 249, 2002, Suppl 3: III, 40) or MRI (Hutchinson M, Raff U., J Neurol Neurosurg Psychiatry. 1999 Dec; 67(6): 815-8).
- Imaging methods such as PET or SPECT (Prunier C, Bezd E et al, Neuroimage. 2003 July; 19(3): 810-6).
- Sensory disorders or behavioural abnormalities, such as sleep and olfactory disorders, in particular, sleep disorders of the type “REM sleep behaviour disorder”, (Henderson, J Neurol Neurosurg Psychiatry 74, 2003, 956) or cognitive abnormalities (Rammsayer, Int J Neurosci. 91, 1997, 45).
- Organic problems such as constipation (Krygowska-Wajs, Funct Neurol 15, 2000, 41).
- Short-term movement anomalies, such as chorea or orthostatic abnormalities.

This thus creates the opportunity to influence the process of the disease at a point when more neurones are still present than is the case at the time of onset of several cardinal motor symptoms of Morbus Parkinson, and to thus protect a quantitatively greater number of neurones. It can be expected that the administration of an effective neuroprotective agent at an early stage will significantly delay the disease process: The earlier a therapy can be initiated, the greater the chances of a long-lasting prevention of the onset of symptoms that lower the quality of life.

There is thus a need for medicaments that are not only able to influence dopaminergic transmission and alleviate the symptoms of Morbus Parkinson in advanced stages, but that are also able to reverse, prevent or at least significantly slow down the progressive destruction of dopaminergic neurones in the early, largely motor-asymptomatic stages of Parkinson’s disease (Dawson, Nature Neuroscience Supplement 5, 2002, 1058).

Rotigotine [(−)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol] is known from the prior art as a dopamine agonist and as a therapeutic agent purely for the symptoms of Parkinson’s disease. WO 02/089777 describes, for example, the transdermal administration of rotigotine to patients with Parkinson’s disease and the associated improvement in the UPDRS (Unified Parkinson’s Disease Rating Scale) score. The
UPDRS score is an important instrument for diagnosing and monitoring the progression and/or therapy of patients with Parkinson’s disease (Fahn S, Elton RL, Members of the UPDRS Development Committee (1987) Unified Parkinson’s Disease Rating Scale. In: Fahn, S, CD Marsden, DB Calne, M Goldstein (eds) Recent Developments in Parkinson’s Disease. Vol. II. Macmillan Healthcare Information, Florham Park (NJ), pages 153-163, 293-304). However, the UPDRS score only records the effect of an active substance on the symptoms of Parkinson’s disease. It does not allow any statements to be made with regard to whether or not an active substance has an influence on the destruction of dopaminergic cells, which is the underlying cause of the symptoms.

Metman et al (Clin Neuropharmacol 24, 2001, 163) also describe the effect of rotigotine on motor disturbances associated with Parkinson’s disease. The treated patients already had pronounced dyskinesias, which were improved by administering rotigotine.

Thus, rotigotine is known from the prior art as a dopamine agonist for the symptomatic treatment of Parkinson’s disease. However, Parkinson medicaments that only have an effect on the symptoms do not promise any advantage with regard to the prophylactic treatment of Parkinson’s disease since they do not have any influence on the destruction of dopaminergic cells or on the progression and/or intensity of the disease.

Experimental tests have, however, now surprisingly shown that rotigotine, which had hitherto only been used for the symptomatic therapy of Parkinson’s disease, has neuroprotective properties and/or promotes the regenerative capacity of neuronal elements such that rotigotine can thus be used as a medicament and/or prophylactic agent for the prevention of dopaminergic cell loss also and in particular in very early stages of Parkinson’s disease or in high-risk patients.

Figures

Fig. 1 shows representative examples of the neuroprotective effect of rotigotine measured on the basis of the density of the dopamine transporters as an indication of the density of the remaining nerve endings in the striatum.

Groups 1 to 7 were treated as follows: Group 1: untreated control group; Group 2: control group treated with a vehicle solution for rotigotine and MPTP; Group 3: MPTP treatment; Group 4: MPTP treatment plus rotigotine 0.3 mg/kg; Group 5: MPTP treatment plus rotigotine 1.0 mg/kg; Group 6: MPTP treatment plus rotigotine 3.0 mg/kg; Group 7: treatment solely with rotigotine (3.0 mg/kg).
Fig. 2 shows dopamine transporter (DAT) binding in the dorsal and ventral part of the striatum in different groups by quantifying the DAT density according to an experiment as shown in Fig. 1. Bar graphs 1 to 7 correspond to groups 1 to 7 as shown in Fig. 1. The groups marked with * displayed a significant decline in DAT binding as compared to the control group 2. The groups marked with # displayed a significant gain in DAT binding as compared to the MPTP-treated Group 3.

Description of the Invention

Apoptotic processes are supposed to play an important role in the destruction of dopaminergic neurones in the pathogenesis of Parkinson’s disease (Barzilai, Cell Mol Neurobiol 21, 2001, 215). Neuroprotective substances that can stop or even reverse dopaminergic cell destruction are thus desired. The MPTP model is thereby deemed to be predictive of the required neuroprotective characteristics (Dawson, Nature Neuroscience Supplement 5, 2002, 1058).

Rotigotine surprisingly shows the desired pharmacological profile in both an acute and a sub-acute MPTP model. The test results suggest that apoptotic processes are prevented by rotigotine.

Rotigotine displays, for example, a neuroprotective effect in a mouse model of Parkinson’s disease: Following the acute administration of MPTP, which causes Parkinson’s syndrome in both humans and monkeys, the number of the degenerating neurones in the acute phase was measured on the one hand (Table 1) and the functional integrity of the striatum in the sub-acute phase was ascertained on the other by determining the density of the dopamine transporter in the terminal nerve endings (Figs. 1 and 2). It could be demonstrated in both cases that rotigotine had a neuroprotective effect: On the one hand, the number of degenerating neurones in the mesencephalon was reduced following the administration of rotigotine and on the other hand, the dopaminergic innervation of the striatum was almost completely maintained or restored.
Table 1: Number of degenerating neurones in the mouse, shown by FluoroJade staining

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of degenerating neurones</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Vehicle-treated control group</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>2: MPTP intoxication</td>
<td>73.5</td>
<td>34.0</td>
</tr>
<tr>
<td>3: MPTP intoxication + rotigotine 0.3 mg/kg</td>
<td>66.7</td>
<td>30.5</td>
</tr>
<tr>
<td>4: MPTP intoxication + rotigotine 1.0 mg/kg</td>
<td>76.8</td>
<td>41.6</td>
</tr>
<tr>
<td>5: MPTP intoxication + rotigotine 3.0 mg/kg</td>
<td>34.9</td>
<td>31.9</td>
</tr>
<tr>
<td>5: MPTP -vehicle + rotigotine 3.0 mg/kg</td>
<td>3.8</td>
<td>4.3</td>
</tr>
</tbody>
</table>

In a pilot study, the neuroprotective effect of rotigotine on monkeys was also examined.

In the model used, which reflects the progressive course of Morbus Parkinson in primates, monkeys (macaques) were injected with subliminal toxic doses of MPTP for several days. Parkinson’s symptoms developed in the model over a period of approximately 2 weeks. As soon as a certain level of damage had been reached, rotigotine was injected daily in a formulation that produced a continuous plasma level over 24 hours. The MPTP injections were stopped as soon as the motor activity had been reduced to a certain extent (approximately 5 days later). The behaviour of the animals was assessed on a daily basis. Six weeks after the start of MPTP administration, the rotigotine injections were stopped and the animals were observed for a further two weeks without treatment. It was observed that the motor activity of the animals clearly improved during treatment and also in the following clearance phase.

A group of animals was killed at the end of both the rotigotine administration and the clearance phase, and the condition of the basal ganglia was histologically and biochemically examined. The density of the nerve endings in the striatum had significantly increased as compared to the untreated animals. The content of pre-pro-enkephalin, which is an indicator of the intact network in the “indirect pathway” of the basal ganglia, showed a tendency towards normalisation following treatment and the clearance phase.

The results show that the neuroprotective potential of rotigotine can also be proven in a primate model of Morbus Parkinson. A neuroprotective effect can therefore also be expected in humans.
Thus, with rotigotine an active substance was provided for therapy, which is ideally suitable for producing a medicament and/or prophylactic agent for the prevention of dopaminergic neurone loss in neurodegenerative diseases.

A subject matter of the present application is therefore the use of rotigotine for the production of a medicament for the treatment or prevention of dopaminergic neurone loss in patients suffering from a neurodegenerative disease that is associated with increased dopaminergic cell destruction or in patients having an increased risk of augmented dopaminergic cell destruction.

Increased dopaminergic neurone loss regularly occurs in patients with Parkinson’s disease, however, it is also frequently observed in other neurodegenerative diseases, for example, in alpha-synucleopathies or in Huntington’s disease as well as in REM sleep disturbances and olfactory disorders.

As compared to the hitherto use of rotigotine, which was limited solely to the symptomatic treatment of Parkinson’s patients with motor disturbances, in particular the prophylactic treatment of individuals in an early stage of Parkinson’s disease and/or who are predisposed to developing Parkinson’s disease owing to genetic or other risks has been developed as a new area of use. As already described above, such individuals profit in particular from the neuroprotective effect of rotigotine since owing to the administration of rotigotine, dopaminergic cell loss is stopped or slowed down at a time when a higher number of dopaminergic neurones are still present than is the case in patients already displaying motor symptoms.

A subject matter of the invention is therefore the use of rotigotine or its salts and prodrugs as a medicament for the prophylactic treatment of dopaminergic cell loss in individuals in whom, before commencement of the prophylactic treatment, at least three of the four cardinal symptoms of Parkinson’s disease from the group bradykinesia, rigidity, resting tremors and postural instability are not yet present or are only rudimentary or partially present.

The individuals can also be apparently healthy individuals whose genetic or epidemic predisposition may not indicate an increased risk of developing Parkinson’s disease.

However, in particular individuals having an increased risk of developing Parkinson’s disease or patients in whom early clinical, clinical/chemical or clinical/physical symptoms of Parkinson’s disease can be detected, but who do not yet display two or more of the
cardinal symptoms of Parkinson's disease, come into consideration for treatment with
rotigotine.

Finally, rotigotine can also be used as a neuroprotective agent if the diagnosis is not clear,
but development of the symptoms towards Parkinson-like neurodegeneration can be
expected.

Prevention of neuronal dopaminergic cell loss is required in particular by

(a) individuals with an increased risk of Parkinson's disease or
(b) individuals with early symptoms of Parkinson's disease.

The terms "Morbus Parkinson" and "Parkinson's disease" are used as synonyms in this
patent application and include idiopathic and genetic Parkinson's disease. The so-called
Parkinson-Plus syndrome as well as secondary Parkinsonism are to be differentiated
therefrom.

The term "cardinal symptoms" of Parkinson's disease is to be understood in this patent
application as one or more of the symptoms of bradykinesia, rigidity, resting tremors and
postural instability.

"Individuals with an increased risk of Parkinson's disease" are to be understood in this
patent application in particular as individuals who do not yet display any detectable
symptoms of Parkinson's disease, but who have certain risk factors.

Such risk factors can be genetic mutations (Nussbaum NEJM 348, 2003, 25). For
example, the parkin gene on chromosome 6q25.2-27 (PARK2) is associated with juvenile
Parkinsonism and occurs more frequently in families with autosomal recessive Parkinson
und Lucking, N. Engl. J. Med. 342, 2000, 1560-7). Other gene loci, for example, PARK6
and PARK7, were also found with increased frequency in families with juvenile,
vanden Duijin, Am. J. Hum. Genet. 69, 2001, 629). The PARK8 gene is, on the other hand,
associated with the late onset of Parkinson's disease (WO 03/076658). Mutations in the
alpha-synuclein gene (PARK1) were detected in families with juvenile, autosomal
In addition to genetic predisposition, environmental influences, such as high exposure to, for example, insecticides (Vanacore, Neurol Sci., Sep; 23 Suppl 2, 2002, page 119) can also represent risk factors.

In this patent application, "individuals with early symptoms of Parkinson’s disease" are to be understood in particular as individuals in whom at least three of the four cardinal symptoms (rigidity, resting tremors, bradykinesia and postural instability) are not yet present, or are only rudimentarily or partially present, but who manifest diagnostically useable early clinical, clinical/biochemical and/or clinical/physical symptoms.

Clinical/biochemical markers can be modifications in the alpha synuclein or neuromelanin pattern (WO 02/31499). Such modifications can be due, for instance, to the expression of genetic variants, for example of alpha synuclein, the development of aggregates or filaments, for example of alpha synuclein, or the increased release from cellular stores, for example, from the cytoplasms of cells that are being destroyed, as is the case with neuromelanin.

Early clinical/physical symptoms can be structural or functional changes to the brain, which can be physically detected, for example, by means of PET and SPECT studies or by means of transcranial sonography (Becker, J Neurol 249, Suppl 3, 2002, III/40; Prunier C, et al., Neuroimage. 2003 Jul; 19(3): 810-6).

Early clinical symptoms can be olfactory disorders, depression, constipation, impairments of visual and cognitive functions or specific forms of sleep disorders, in particular of the type “REM sleep behaviour disorders”, whereby a combination of different tests can also be used for early diagnosis (Becker, J Neurol 249, Suppl 3, 2002, III/40; Stern, Annals of Neurol 56, 2004, 169).

As already discussed above, approximately 70 to 80% of the dopaminergic neurones of the substantia nigra have already been destroyed by the time at least two of the four cardinal symptoms have manifested themselves for the first time. In order to effectively use the surprising neuroprotective potential of rotigotine, the prophylactic treatment of the patients is therefore preferably initiated at a stage when the patients have a lower loss of dopaminergic cells of the substantia nigra (SN). Individuals displaying just one or none of the cardinal symptoms of Parkinson’s disease in a clearly pronounced form are therefore preferably treated with rotigotine.

Individuals displaying a dopaminergic cell loss in the SN of less than 70%, 60%, 50% and particular preferred of less than 40%, 30%, 20% or 10% are preferably treated.
Two scores can be used as aids for diagnosing and controlling the therapy of patients already displaying noticeable motor disturbances, i.e. the UPDRS score and the Hoehn and Yahr score.

In a preferred aspect of the invention, the group of patients prophylactically treated with rotigotine has a modified Hoehn and Yahr score of 0 to 2, particularly preferred of 0 to 1 and especially preferred of 0.

**Table 2: Modified stage determination according to Hoehn, The natural history of Parkinson’s disease in the pre-levodopa and post-levodopa eras. Neurologic Clinics 10, 1992, 331**

| Stage 0 | No sign of disease. |
| Stage 1 | Unilateral disease. |
| Stage 1.5 | Unilateral plus axial involvement. |
| Stage 2 | Bilateral disease without impairment of balance. |
| Stage 2.5 | Mild bilateral disease with recovery on pull test. |
| Stage 3 | Mild to moderate bilateral disease: slight postural instability; physically independent. |
| Stage 4 | Severe disability; still able to walk or stand unaided. |
| Stage 5 | Wheelchair-bound or bedridden unless aided |

Patients with a UPDRS score, part III (see embodiment 5), of at least 10 are normally classified as patients who can be considered for dopaminergic therapy. However, the group of patients suitable for benefiting from the neuroprotective effect of rotigotine preferably has a very low or undetectable motor UPDRS score (part III). Within the meaning of the present invention, the prophylactic treatment with rotigotine should therefore preferably be carried out on patients having a UPDRS motor score of less than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1. It is particularly preferred for the patients to still not display any motor disturbances at all.

The terms “prevention”, “prophylaxis” and “prophylactic treatment” are used as synonyms in this patent application. They include the administration of a medicament to individuals in whom dopaminergic cell loss is to be expected or has already occurred. These are, in particular, patients in whom at least three of the four cardinal symptoms of Parkinson’s disease (rigidity, resting tremors, bradykinesia, postural instability), are not yet present, or are only rudimentarily or partially present, in order to prevent or delay the appearance or significant development of the motor symptoms of Parkinson’s disease and/or further dopaminergic neurone loss, particularly in the substantia nigra. The
individuals to be prophylactically treated preferably do not yet display any of the cardinal symptoms in a clearly pronounced form. The individuals to be prophylactically treated preferably have a UPDRS score of less than 10, less than 9, 8, 7 or 6 and particularly preferred of less than 5, 4, 3, 2 or 1.

In this patent application, "prodrugs" of rotigotine are to be understood in particular as compounds that are cleaved, converted or metabolised into rotigotine in the human body in a therapeutically effective amount, in particular in the plasma or during the passage through the skin or mucous membrane.

Rotigotine has the formula

![Rotigotine formula](image)

In particular derivatives of the phenolic hydroxy group thus come into consideration as prodrugs, for example, esters, e.g. arylcarbonyl esters, alkylcarbonyl esters or cycloalkylcarbonyl esters, in particular alkylcarbonyl esters and cycloalkylcarbonyl esters with up to 6 carbon atoms; carbonates; carbamates; acetics; ketals; acyloxyalkyl ethers; phosphates; phosphonates; sulphates; sulphonates; thiocarbonyl esters; oxythiocarbonyl esters; thio carbamates; ethers and silyl ethers.

The term "alkylcarbonyl esters" includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(O)-alkyl.

The term "cycloalkylcarbonyl esters" includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(O)-cycloalkyl.

The term "arylcarbonyl esters" includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(O)-aryl.

The term "carbonates" includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(O)-O-R.
The term “carbamate” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(O)-NRR1, –C(O)-NH-R1, or –C(O)-NH₂.

The term “acetals” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –CH(OR)R₁.

The term “ketals” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(OR)R₁R₂.

The term “acyloxyalkyl ethers” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –CHR-O-C(O)-R₁ or CH₂-O-C(O)-R₁.

The term “phosphate” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –P(O₂H)OR.

The term “phosphonate” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –P(O₂H)R.

The term “sulphate” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –S(O)₂OR.

The term “sulphonate” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –S(O)₂R.

The term “thiocarbonyl esters” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(=S)-R.

The term “oxythiocarbonyl esters” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(=S)-O-R.

The term “thiocarbamate” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –C(=S)-NRR₁, –C(=S)-NH-R₁ or –C(=S)-NH₂.

The term “ethers” includes compounds in which the oxygen atom of the rotigotine is bound in each case to the group –R.

In the above definitions of the prodrugs, R, R₁ and R₂ are each independently selected from hydrogen, alkyl, cycloalkyl or aryl, and preferably from the group C1-6 alkyl, C3-10 cycloalkyl and phenyl.
R3 is alkyl, in particular C1-6 alkyl.

"Alkyl" can be a branched or non-branched alkyl group, which preferably has 1 to 10 C-atoms, particularly preferred 1 to 6 C-atoms. Alkyl groups can also be substituted with one or more substituents, for example with halogen.

"Cycloalkyl" is an alkyl group that can consist of only pure ring-forming C-atoms or can optionally have other branching C-atoms. Preferred chain lengths are 3 to 10, particularly preferred 4 to 8 or 4 to 6 C-atoms.

"Aryl" is preferably phenyl. Phenyl can possibly also be substituted at one or more positions, for example, with alkoxy, alkyl, halogen or nitro.

The production of prodrugs by reacting rotigotine with corresponding reactive precursors such as acid chlorides, acid anhydrides, carbamyl chlorides, sulphonyl chlorides etc. is known to the person skilled in the field of clinical chemistry and can be seen in pertinent technical literature. Examples of literature are Bundgaard: Design of prodrugs, Elsevier, Amsterdam, 1985; Higuchi and Stella: Pro-drugs as novel drug delivery systems in American Chemical Society, Washington DC, 1975; Sloan: Prodrugs – Topical and Ocular Drug Delivery, Ed: M. Dekker, 1992; Roche: Design of biopharmaceutical properties through prodrugs and analogs, Washington, DC, 1977.

Various prodrugs of the racemate of Rotigotine (N-0437) are described, for example, in Den Haas et al., Naunyn-Schmiedeberg's Arch Pharmacol 342, 1990, 655; Den Haas et al., Naunyn-Schmiedeberg's Arch Pharmacol. 341, 1990, 186 and Den Haas et al., J Pharm Pharmacol 43, 1991, 11.

The basic suitability of a rotigotine derivative as a prodrug can be determined by incubating the respective compound under defined conditions with an enzyme cocktail, a cell homogenate or an enzyme-containing cell fraction and measuring the resulting rotigotine. A suitable enzyme mixture is contained, for example, in the S 9 liver preparation of the firm Gentest, Woburn, Ma., USA.

Incubation can alternatively take place with fresh blood or plasma or even with a homogenate of the hypodermis in order to demonstrate a liver-independent metabolism of the prodrugs into active components. For transdermal application, an in vitro examination of the permeation on excised skin is necessary. The final proof of suitability
and potential effectiveness in the disease models is obtained by determining in the plasma the 2-N-propylamino-5-hydroxytetralins formed from the prodrug.

In vivo, a prodrug should release so much rotigotine that a therapeutically/prophylactically effective steady state concentration of rotigotine is achieved in the plasma. Rotigotine concentrations of between 0.01 and 50 ng/mL, preferably between 0.05 ng and 20 ng/mL and particularly preferred between 0.1 and 10 ng/mL plasma, are thereby considered to be effective concentrations.

Rotigotine is the S(-)-enantiomer of 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]-amino]-1-naphthol. This means that according to the invention, the proportion of (R)-enantiomer, which inactive in Parkinson’s models, in the medicament is low. The (R)-enantiomer is preferably present in the medicament in a proportion of < 10 mol%, particularly preferred in a proportion of < 2 mol% and especially preferred in a mole proportion of < 1 %, based on the total amount of rotigotine.

Rotigotine and its prodrugs can be present in the medicament as free bases or in the form of physiologically acceptable salts, for example, in the form of the hydrochloride.

“Physiologically acceptable salts” include non-toxic addition salts of rotigotine with organic or inorganic acids. A preferred example of a suitable salt is the HCl salt.

There are many methods of application available for administering rotigotine and its prodrugs, which the person skilled in the art can select and adapt depending on the need, condition and age of the patient, the required dosage and the desired application interval.

A preferred mode of administering rotigotine is transdermal administration. The form of administration may, in principle, be selected from, for example, an ointment, a paste, a spray, a film, a plaster or an iontophoretic device.

Rotigotine is preferably applied to the skin of the patient in plaster form, with the active substance preferably being present in a matrix of adhesive polymer, for instance a self-adhesive polysiloxane. Examples of suitable transdermal formulations can be found in WO 99/49852, WO 02/89777, WO 02/89778, WO 2004/058247 and WO 2004/012721 as well as in embodiment 1. Such a form of administration enables a substantially constant plasma level to be established and therefore a constant dopaminergic stimulation over the entire application interval (WO 02/89778; Metman, Clinical Neuropharmacol. 24, 2001, 163).
If, on the other hand, a medicament in the form of a subcutaneous or intramuscular depot form is desired, rotigotine may be suspended, for example as a salt crystal, for instance as crystalline hydrochloride, in a hydrophobic anhydrous medium and injected, such as described in WO 02/15903 and in embodiment 2.

Rotigotine can basically also be administered in the form of microcapsules, microparticles or implants based on biodegradable polymers, such as described, for example, in WO 02/38646.

Other conceivable forms of administering rotigotine and its prodrugs are transmucosal formulations, for example sublingual sprays, rectal formulations or aerosols for pulmonary administration.

Suitable dosages of rotigotine are between 0.05 and approximately 50 mg/day, with daily doses of preferably between 0.1 and 40 mg and in particular of between 0.2 and 20 mg/day being administered. Dosage can thereby take place in a gradually increasing manner, i.e. the treatment may optionally start with low doses which are then increased until the maintenance dose is reached.

It is clear to the person skilled in the art that the dosage interval may vary depending on the applied quantity, the mode of application and the daily requirement of the patient. Thus, a transdermal form of application may be designed, for example, for administration once a day, once every three days or once every seven days, whilst a subcutaneous or intramuscular depot can make it possible to administer injections, for example, in one-weekly, two-weekly or four-weekly cycles.

Other active substances which prevent the progression of dopaminergic cell loss can also be present in the neuroprotective medicament in addition to rotigotine.

Examples hereof are substances with an anti-apoptotic effect (minocycline, FK-506, cyclosporine A, zVAD) as well as neurotrophins such as, for example, Glial-cell-derived neurotrophic factor (GDNF).

In a combination preparation, a sequential administration can be achieved, for example, in that an administration form, for example an oral tablet, has two different layers with differing release profiles for the different pharmaceutically active ingredients. It is clear to the person skilled in the art that various forms of administration and application patterns are conceivable within the context of the present invention, which all form subject matter of the invention.
A further subject matter of the application is a kit for the early diagnosis and treatment of Morbus Parkinson. Such a kit contains (a) a diagnostic agent that enables the diagnosis of Parkinson’s disease and/or the predisposition to develop Parkinson’s disease at an early or asymptomatic stage as well as (b) a pharmaceutical formulation containing rotigotine, its salts or prodrugs for the treatment or prophylaxis of dopaminergic cell loss.

Such a kit may comprise, for example:

(a) an agent or a diagnosis kit for detecting neuromelanin,
(b) a pharmaceutical formulation containing rotigotine, its salts and prodrugs.

In another embodiment of the invention, the kit may contain:

(a) an agent or a diagnosis kit for detecting semaphorin 3,
(b) a pharmaceutical formulation containing rotigotine, its salts and prodrugs.

In another embodiment of the invention, the kit may contain:

(c) an agent or a diagnosis kit for detecting alpha-synuclein and/or its aggregates,
(d) a pharmaceutical formulation containing rotigotine, its salts and prodrugs.

In a further embodiment of the invention, the kit may contain:

(a) an agent or a diagnosis kit for genetically detecting a mutation associated with the appearance of Parkinson’s disease and/or an allele associated with the more frequent appearance of Parkinson’s disease, in particular, from the group of PARK genes 1, 2, 3, 4, 5, 6, 7 or 8 as well as the gene loci CYP2D6-B and GSTM1,
(b) a pharmaceutical formulation containing rotigotine, its salts and prodrugs.

**Embodiments:**

**Embodiment 1: Rotigotine Plaster**

1.8 g of rotigotine (free base) were dissolved in 2.4 g of ethanol and added to 0.4 g of Kollidon 90F (dissolved in 1 g of ethanol). This mixture was added to a 74% solution of silicone polymers (8.9 g of BioPSA 7-4201 + 8.9 g of BIO-PSA 7-4301 [Dow Corning]) in heptane. Following the addition of 2.65 g of petrol ether, the mixture was stirred for 1
hour at 700 rpm in order to obtain a homogeneous dispersion. Following lamination on polyester, it was dried at 50°C. The final weight of the plaster was 50 g/cm².

**Embodiment 2: Rotigotine Depot Suspensions**

(a) 1411.2 g of Miglyol 812 were weighed into a Duran flask. 14.4 g of Imwitor 312 were added to the Miglyol and then heated for 30 minutes to 80°C whilst being stirred. The clear solution was cooled to room temperature and filtered.

(b) 1188 g of the solution produced in (a) were transferred into a glass laboratory reactor, 12 g of rotigotine were added and homogenised for 10 minutes under nitrogen with an Ultraturrax at 10,000 rpm. The suspension was decanted into brown glass bottles whilst the Ultraturrax was running (2,000 rpm).

**Embodiment 3: Sub-Acute MPTP Model**

For the purpose of intoxication, 80 mg/kg of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) were administered to mice (in doses of 20 mg/kg at two-hour intervals, groups 3 to 6 in Figs. 1 and 2), which led to the degeneration of approximately 50 to 60% of the neurones of the substantia nigra (maximum degeneration in group 3 in Figs. 1 and 2). Rotigotine was administered daily for 7 days in doses of 0.3, 1 or 3 mg/kg respectively as the so-called “slow-release formulation” (see embodiment 2) (groups 4 to 6 in Figs. 1 and 2). A group of MPTP-treated animals (group 3) was given a rotigotine vehicle solution (see embodiment 2 without rotigotine HCl) and served as a reference. Groups 1, 2 and 7 served as controls, whereby group 1 did not receive any treatment at all, group 2 was treated with the vehicle solutions for MPTP and rotigotine and group 7 received exclusively rotigotine. The animals were killed on day 8 and their brains were removed and frozen. The frozen sections were incubated with 100 pm [125I] PE2I ([125I]- (E)-N(3-iodoprop-2-enyl)-2β-carboxymethyl-3β-(4' -methylphenyl)-nortropane) in phosphate buffer, pH 7.4, in order to mark the amount of dopamine transporters still present in the striatum, which indicates the number of functioning nerve endings. Rotigotine improved the survival of the neurones and their nerve endings depending on the dosage. This is a clear indication of the neuroprotective properties of the substance (Figs. 1 and 2).

**Embodiment 4: Acute MPTP Model (Including Apoptosis)**

For the purpose of intoxication, 80 mg/kg of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) were administered to mice (in doses of 20 mg/kg at two-hour intervals), which led to the degeneration of approximately 50 to 60% of the neurones of
the substantia nigra. Approximately 16 hours beforehand, rotigotine was administered in
doses of 0.3, 1 or 3 mg/kg respectively, as the so-called “slow-release formulation”.
Diffusion and absorption latencies led to rotigotine then being optimally available when
MPTP was administered. The animals were killed after 24 hours and their brains fixed.
The brain sections were stained with FluoroJade to identify degenerating cells. The
immunohistochemical marking of tyrosine-hydroxylase helped to identify dopaminergic
neurones. The staining of tyrosine hydroxylase did not display any differences between
the treated and untreated animals; staining with FluoroJade showed a large number of
degenerating neurones; the neurones had, however, not yet been completely removed; this
suggests that the cell destruction occurs apoptotically. The number of degenerating
neurones was approximately 50% less following application of rotigotine, which further
demonstrates the neuroprotective property of the substance (Table 1).

Embodiment 5: Determination of the Motor UPDRS Score

The motor UPDRS score (part III of the UPDRS score) is determined by examining the
patient using criteria 18 to 31 as given below in Table 2, with the point scores resulting for
each of the criterion being respectively added together.

III. MOTOR EXAMINATION

18. Speech:
□ 0 - Normal.
□ 1 - Slight loss of expression, diction and/or volume.
□ 2 - Monotone, slurred but understandable; moderately impaired.
□ 3 - Marked impairment, difficult to understand.
□ 4 - Unintelligible.

19. Facial Expression:
□ 0 - Normal.
□ 1 - Minimal hypomimia, could be a normal “poker face”.
□ 2 - Slight but definitely abnormal diminution of facial expression.
□ 3 - Moderate hypomimia; lips parted some of the time.
□ 4 - Masked or fixed face with severe or complete loss of expression; lips parted by
7 mm.
20. Tremor at rest: (F = face, RH = right hand, LH = left hand, RF = right foot, LF = left foot)

<table>
<thead>
<tr>
<th>F</th>
<th>RH</th>
<th>LH</th>
<th>RF</th>
<th>LF</th>
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</table>
| 0 |    |    |    |    | Absent.
| 1 |    |    |    |    | Slight and infrequently present.
| 2 |    |    |    |    | Mild in amplitude and persistent; or moderate in amplitude but only intermittently present.
| 3 |    |    |    |    | Moderate in amplitude and present most of the time.
| 4 |    |    |    |    | Marked in amplitude and present most of the time.

21. Action or Postural Tremor of the Hands: (R = right, L = left)

<table>
<thead>
<tr>
<th>R</th>
<th>L</th>
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</table>
| 0 |    | Absent.
| 1 |    | Slight; present with action.
| 2 |    | Moderate in amplitude, present with action.
| 3 |    | Moderate in amplitude, present with posture holding as well as action.
| 4 |    | Marked in amplitude; interferes with eating.

22. Rigidity: (Judged on passive movement of major joints on a patient in the sitting position. Cogwheeling can be ignored). (N = neck, RUE = right upper extremity, LUE = left upper extremity, RLE = right lower extremity, LLE = left lower extremity).

<table>
<thead>
<tr>
<th>N</th>
<th>RUE</th>
<th>LUE</th>
<th>RLE</th>
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</table>
| 0 |    |    |    |    | Absent.
| 1 |    |    |    |    | Slight or detectable only when activated by mirror-image or other movements.
| 2 |    |    |    |    | Mild to moderate.
| 3 |    |    |    |    | Marked, but full range of motion still achievable.
| 4 |    |    |    |    | Severe, difficulty in carrying out all movements.

23. Finger Taps: (Patient taps thumb against index finger in rapid succession with maximum possible amplitude and separately with each hand). (R = right, L = left).

<table>
<thead>
<tr>
<th>R</th>
<th>L</th>
</tr>
</thead>
</table>
| 0 |    | Normal.
| 1 |    | Slight slowing and/or reduction in amplitude.
| 2 |    | Moderately restricted. Distinct and premature fatiguing. Movement may occasionally be interrupted.
24. Hand Movements: (Patient opens and closes the hands in rapid succession with greatest possible amplitude and separately with each hand). (R = right, L = left).
R  L
☐ ☐ 0 - Normal.
☐ ☐ 1 - Slight slowing and/or reduction in amplitude.
☐ ☐ 2 - Moderately restricted. Distinct and premature fatiguing. Movement may occasionally be interrupted.
☐ ☐ 3 - Severely restricted. Delayed start of the movements or interruption of continuous movements.
☐ ☐ 4 - Can barely perform the task.

25. Rapid Alternating Movements of the Hands: (pronation/supination movements of the hands, vertically or horizontally, with largest possible amplitude, both hands simultaneously).
R  L
☐ ☐ 0 - Normal.
☐ ☐ 1 - Slight slowing and/or reduction in amplitude.
☐ ☐ 2 - Moderately restricted. Distinct and premature fatiguing. Movement may occasionally be interrupted.
☐ ☐ 3 - Severely restricted. Delayed start of the movements or interruption of continuous movements.
☐ ☐ 4 - Can barely perform the task.

26. Leg Agility: (Patient taps heel on the ground in rapid succession thereby lifting the entire leg. Amplitude should be at least 7.5 cm).
R  L
☐ ☐ 0 - Normal.
☐ ☐ 1 - Slight slowing and/or reduction in amplitude.
☐ ☐ 2 - Moderately restricted. Distinct and premature fatiguing. Movement may occasionally be interrupted.
☐ ☐ 3 - Severely restricted. Delayed start of the movements or interruption of continuous movements.
☐ ☐ 4 - Can barely perform the task.
27. Rising from Chair: (Patient attempts to rise from a straight-back wooden or metal chair with arms folded across chest).
□ 0 - Normal.
□ 1 - Slow; may need more than one attempt.
□ 2 - Pushes self up using arms of seat.
□ 3 - Tends to fall back and may possibly have to make several attempts, but can rise without assistance.
□ 4 - Unable to rise without assistance.

28. Posture:
□ 0 - Normal erect.
□ 1 - Not quite erect, slightly stooped posture; could be normal for an older person.
□ 2 - Moderately stooped posture, definitely abnormal; can be leaning slightly to one side.
□ 3 - Severely stooped posture with kyphosis; can be leaning moderately to one side.
□ 4 - Marked flexion with extremely abnormal posture.

29. Gait:
□ 0 - Normal.
□ 1 - Walks slowly, may shuffle a few short steps, but no festination or propulsion.
□ 2 - Walks with difficulty, but requires little or no assistance; possibly slight festination, short steps or propulsion.
□ 3 - Severe disturbance of gait, requires assistance.
□ 4 - Cannot walk at all, even with assistance.

30. Postural Stability: (Response to sudden rearwards displacement caused by pulling on the patient’s shoulders whilst patient is erect and has their eyes open and feet slightly apart. Patient is prepared.)
□ 0 - Normal.
□ 1 - Retropulsion, but recovers unaided.
□ 2 - No postural response; would fall if not caught by examiner.
□ 3 - Very unstable, tends to lose balance spontaneously.
□ 4 - Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia: (Combination of slowness, hesitancy, decreased arm-swing, small movement amplitude and poverty of movement in general.)
□ 0 - None.
1 - Minimal slowing, movement is intentional; could be normal for some persons. Possibly reduced amplitude.
2 - Slight slowing and poverty of movement, which is clearly abnormal. Alternatively also reduced amplitude.
3 - Moderate slowing and poverty of movement or reduction in amplitude.
4 - Marked slowing, poverty of movement or reduction in amplitude.

Embodiment 6: In Vitro Conversion of a Prodrug into the Active Substance

The microsome fraction that contains the essential metabolising enzymes is obtained from the liver cell homogenates of a human, monkey, dog, rat or mouse by means of differential centrifugation; the cytoplasmatic fraction can alternatively also be obtained. The subcellular fraction is suspended with a buffer such that a solution having a defined protein content is obtained. Following the addition of 1 μM of the prodrug to be tested, incubation takes place at 37°C for 60 min. Rotigotine is then quantified by means of HPLC/UV or also by means of HPLC/MS and is related to the used amount. The concentration or time series are examined for detailed analyses.
Patent Claims

1. Use of rotigotine, its salts or prodrugs thereof for producing a medicament for the treatment or prophylaxis of diseases associated with increased dopaminergic cell destruction,

wherein the treatment or prophylaxis is performed on individuals who are selected from the group of

(a) individuals without symptoms of Parkinson’s disease but with an increased risk of developing Parkinson’s disease, and

(b) individuals with early symptoms of Parkinson’s disease, in whom at least three of the four cardinal symptoms of Parkinson’s disease (rigidity, resting tremors, bradykinesia, postural instability) are not yet present.

2. Use according to claim 1, wherein the prophylactically treated disease associated with increased dopaminergic cell destruction is Parkinson’s disease.

3. Use according to claim 1, wherein the disease associated with increased dopaminergic cell destruction is selected from alpha-synucleopathies, Huntington’s disease, REM sleep disturbances and olfactory disorders.

4. Use according to one of the preceding claims, wherein the individuals display one or more of the following early clinical symptoms: olfactory disorders, depression, sleep disorders of the type “REM sleep behaviour disorders”, constipation and short-term movement anomalies.
5. Use according to one of the preceding claims, wherein the individuals display a mutation in a PARK gene and/or modifications to the alpha-synuclein or neuromelanin pattern.

6. Use according to one of the preceding claims, wherein the individuals display a dopaminergic cell loss in the substantia nigra of less than 60% before commencement of medicament administration.

7. Use according to one of the preceding claims, wherein the individuals have a motor UPDRS score of less than 9 before commencement of medicament administration.

8. Use according to one of the preceding claims, wherein the individuals have a Hoehn-Yahr score of 0.

9. Use according to one of the preceding claims, wherein the medicament is provided for parenteral, transdermal or mucosal administration.

10. Use according to one of the preceding claims, wherein the rotigotine is administered in a dose of 0.05 to 50 mg per day.

11. Use according to one of the preceding claims, wherein the prodrug is selected from the group of esters, carbamates, acetals, ketals, phosphates, phosphonates, sulphates, sulphonates and silyl ethers.

12. Use according to one of claims 1 to 10, wherein the prodrug is selected from the group of carbonates, acyloxyalkyl ethers, thiocarbonyl esters, oxythiocarbonyl esters, thiocarbamates and ethers.
13. Use according to one of the preceding claims, wherein the medicament comprises, in addition to rotigotine, at least one other active substance which prevents the progression of dopaminergic cell loss, such as, for example, substances with an anti-apoptotic effect or neurotrophins.

14. A kit for the diagnosis and preventative treatment of Parkinson's disease, comprising

(a) a diagnostic agent that enables the diagnosis of Parkinson's disease and/or the predisposition to develop Parkinson's disease at an early or asymptomatic stage and

(b) a pharmaceutical formulation comprising rotigotine, its salts or prodrugs.

15. The kit according to claim 14, wherein the diagnostic agent (a) is selected from:

(i) an agent or a diagnosis kit for detecting neuromelanin
(ii) an agent or a diagnosis kit for detecting semaphorin 3
(iii) an agent or a diagnosis kit for detecting alpha-synuclein and/or its aggregates or
(iv) an agent or a diagnosis kit for genetically detecting a mutation associated with the appearance of Parkinson's disease and/or an allele associated with the more frequent appearance of Parkinson's disease.
Application number: numéro de demande: EP04/14655

Figures: 1, 2

Pages:

DRW-IP

Unscannable items received with this application
(Request original documents in File Prep. Section on the 10th Floor)

Documents reçus avec cette demande ne pouvant être balayés
(Commander les documents originaux dans la section de préparation des dossiers au 10ème étage)