THERAPEUTIC USE OF MELATONIN

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a method and pharmaceutical formulation for treating tardive dyskinesia

Tardive dyskinesia (TD) is an involuntary movement disorder, which develops in a high percentage of patients who have been treated with neuroleptic drugs. A number of articles have appeared in the literature suggesting an inverse relationship between melatonin secretion and the incidence of TD symptoms. However, to the best of our knowledge, in only one instance has administration of exogenous melatonin been attempted in this connection, in which it was found that whereas treatment with haloperidol of pinealectomized rats resulted in significantly more severe movement disorder than in unoperated control rats, subsequent administration of melatonin (4 mg, i.p.) was associated with a non-significant reduction of the severity of movements within one hour (Sabdyk, R., et al., Int. J. Neurosci., 1989, 48 (3-4): 303-8). The amount of melatonin used in this non-significant result was equivalent to more than 1000 mg for a 70 kg human, so that it is not surprising that subsequent attempts at TD therapy have avoided the use of exogenous melatonin. In U.S. Patent No. 5,691,324 to Sandyk, R., for example, TD is one of a number of conditions, related to deficient serotonin transmission and impaired melatonin function, which is treated by administering to a patient a composition which increases serotonin neurotransmission, followed by applying a magnetic field to the brain. The entire contents of U.S. Patent No. 5,691,324 are incorporated herein by reference.

It has now surprisingly been found, in relation to tardive dyskinesia, that exogenous melatonin produces a significant therapeutic effect in humans, at a dosage rate which is at least one order of magnitude lower (taking into account the average weight of humans in relation to laboratory animals) than that used in the report in .Int. J. Neurosci., mentioned above.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a pharmaceutical formulation which comprises, in addition to at least one carrier, diluent or adjuvant, at least one neuroleptic compound in an amount effective to exert a neuroleptic effect in a patient requiring such treatment, and melatonin in an amount effective to ameliorate or prevent symptoms of tardive dyskensia developing in the patient.

In another aspect, the invention provides use of melatonin in the manufacture of a medicament for the prevention or treatment of symptoms of tardive dyskensia in a patient. The medicament preferably takes the form of a pharmaceutical formulation, which includes at least one of the following additional components (a) and (b): (a) at least one carrier, diluent or adjuvant. (b) at least one neuroleptic compound in an amount effective to exert a neuroleptic effect in a patient requiring such treatment. Further in accordance with the invention, a method for preventing or treating symptoms of tardive dyskensia in a patient, comprises administering melatonin to a patient exhibiting such symptoms or liable otherwise to develop such symptoms, in an amount effective to ameliorate or prevent symptoms of tardive dyskensia developing in the patient.

DETAILED DESCRIPTION OF THE INVENTION

The medicament/pharmaceutical formulation may be administered in any convenient form, such as one adapted for oral, rectal, parenteral or transdermal administration. It may be e.g. in unit dosage form. In a particular embodiment, the melatonin is in the form of a controlled release formulation, wherein the melatonin is preferably released at a predetermined controlled rate.

The amount of melatonin presently contemplated for use in preventing or treating tardive dyskinesia will be the amount found to be effective for this purpose, presently believed to be, in the case of oral administration, more than 0.5 mg and no more than 100 mg daily, e.g. 0.5-50 mg, preferably 2.5-20 mg, and for parenteral or transdermal administration, between 0.1 and 50 mg. In accordance with the invention, an effective amount of melatonin may be formulated e.g. together with an effective dosage of a neuroleptic drug. The present medicament/pharmaceutical formulation may comprise also at least one melatonin receptor modifier and/or melatonin profile modifier.

Once the concept of the present invention for treatment or prevention of TD using melatonin is known according to the present invention, no inventive skill would be required to ascertain the range of effective amounts of melatonin for the present purpose, for various routes of administration. Where the pharmaceutical formulation includes at least one neuroleptic compound, this may for example be selected from such compounds containing at least one of the following ring systems, namely, piperidine, pirperazine, morpholine, 5,6,7,8-tetrahydroindole, phenothiazine and thioxanthene. Exemplary neuroleptic compounds are chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, thiothixene, haloperidol, loxapine, molindone (c.f. Table 1), and clothiapine, clozapine, olanzapine, risperidone and zuclopenthixol acetate, and their pharmaceutically acceptable salts).

Table 1: Neuroleptic Compounds

Compound	Daily Dosage* possible	usual	Modes of Administration	Intramuscular single dosage*
Chlorpromazine+	25-2000	300-800	oral; parenteral, rectal, SR	20-50
Triflupromazine+	25-300	100-150	oral, parenteral	20-60
Mesoridazine besylate	25-300	75-300	oral, parenteral	25
Piperacetazine	5-200	20-160	oral	---
Thioridazine+	20-800	200-600	oral	—
Acetophenazine maleate	20-600	60-120	oral	---
Fluphenazine+	0.5-30	1-20	oral, parenteral	1.25-2.5
Perphenazine	4-64	8-32	oral, parenteral, SR	5-10
Trifluoperazine+	2-60	6-20	oral, parenteral	1-2
Chlorprothixene	30-600	50-400	oral, partenteral	25-50
Thiothixene+	6-60	6-30	oral, parenteral	2-4
Haloperidol	1-100	6-20	oral, parenteral	2-5
Loxapine succinate	20-250	60-100	oral, parenteral	12.5-50
Molindone+	12-225	50-100	oral	—

*mg +hydrochloride SR=sustained release (oral)

The invention will be illustrated by the following Examples.

Example 1

The following ingredients are mixed together and the mixture was compressed in a 7 mm cylindrical punch, at 2.5 tons, in order to make controlled release tablets: chlorpromazine hydrochloride (275 mg/tablet), melatonin (5 mg/tablet), and Eudragit™ RS 100 acrylic resin carrier (Rohm Pharma) and lactose in an approximately 1:1 ratio by weight. While this formulation should be administered in accordance with a physicians instructions, it is presently contemplated that two such tablets taken two hours before bedtime would be appropriate.

Example 2

The following ingredients are mixed together and the mixture was compressed in a 7 mm cylindrical punch, at 2.5 tons, in order to make controlled release tablets: perphenazine (10 mg/tablet), melatonin (5 mg/tablet), and

Eudragit™ RSPO acrylic resin carrier (Rohm Pharma), lactose and calcium hydrogen phosphate in an approximately 2:1:2.5 ratio by weight. While this formulation should be administered in accordance with a physicians instructions, it is presently contemplated that two such tablets taken two hours before bedtime would be appropriate.

Example 3

The effect of melatonin on tardive dyskinesis was determined on a trial population of 22 patients, of whom 6 were schizoaffective and 16 were paranoid schizophrenics. All patients, who had been receiving long-term neuroleptic treatment, were diagnosed according to DSM IV. They consisted of 11 men and 11 women, age 39±15 years, age range 17-61 years, of whom 19 completed the trial and are included in the results. In a randomized, double blind, crossover manner, subjects were given daily either 2 x 5 mg melatonin in a controlled-release formulation (Circadin™, Neurim Pharmaceuticals, Israel), two hours before bedtime, or a placebo of identical appearance, for a period of six weeks, with a four week placebo wash-out between two treatment periods. Besides the melatonin or placebo, each patient received, respectively, one of the following daily doses (mg) of neuroleptic, or in two cases no neuroleptic drug: chlorpromazine (250), clothiapine (20, 80 or 160), clozapine (200, 400 or 550), haloperidol (5, 15 or 20), olanzapine (10 or 15), perphenazine (4, 8, 12, 32 or 32), risperidone (4) or zuclopenthixol acetate (4 or 20). During the last week of each treatment period, TD severity was assessed using the Abnormal Involuntary Movements Scale (AIMS) and comparisons were made between placebo or melatonin treatments, and baseline. The results are shown in tables 2 and 3.

Table 2: results of T-tests for various AIMS parameters

AIMS sub-scale	Parameter	T-test (t_{21})§	p
1	facial and oral movements	-1	0.33
2	lips and perioral area	-3.92	<0.001*
3	jaw	-1.14	0.27
4	tongue	-0.81	0.43
5	arms, hands	-1.78	0.09
6	legs, knees	-2.81	0.01*
7	neck, shoulder	-2.49	0.02*
8	severity of abnormal movements	-1.82	0.08
9	implication due to abnormal movements	-1.14	0.27
10	patient's awareness	delta = 0	
11	problem with teeth	delta = 0	

§ comparison of the baseline/administration difference, placebo vs. melatonin

* significant outcome

Table 3: results of studies on the effect of melatonin on tardive dyskinesis

AIMS sub-scale	Intensity of Movements (standard deviation)			
	baseline .. placebo		baseline .. melatonin	
1	2.14 (0.89)	2.00 (0.82)	2.18 (0.80)	1.91 (0.87)
2	3.27 (0.70)	3.27 (0.70)	3.50 (0.74)	3.00 (0.98)
3	3.00 (1.07)	2.73 (1.12)	3.09 (1.11)	2.68 (1.13)
4	3.55 (0.67)	3.32 (0.65)	3.50 (0.67)	3.18 (0.80)
5	1.73 (0.83)	1.64 (0.79)	1.91 (0.92)	1.50 (0.74)
6	1.23 (0.53)	1.23 (0.53)	1.55 (0.91)	1.27 (0.63)
7	1.18 (0.50)	1.14 (0.47)	1.55 (1.06)	1.27 (0.70)
8	3.36 (0.73)	3.27 (0.70)	3.50 (0.74)	3.27 (0.88)
9	3.09 (0.81)	2.95 (0.79)	3.00 (0.87)	2.73 (0.88)
10	1.73 (0.70)	1.73 (0.70)	1.73 (0.70)	1.73 (0.70)
11	1.91 (0.29)	1.91 (0.29)	1.91 (0.29)	1.91 (0.29)

Conclusion. The present study revealed a highly significant ($p<0.0001$, MANOVA) decrease, i.e. improvement, after melatonin administration compared with placebo (-3 ± 2.1 and -1 ± 1.3, respectively).

While the present invention has been particularly described with reference to certain embodiments, it will be apparent to those skilled in the art that many modifications and variations may be made. The invention is accordingly not to be construed as limited in any way by such embodiments, rather its concept is to be understood according to the spirit and scope of the claims which follow.

CLAIMS

1. A pharmaceutical formulation which comprises, in addition to at least one carrier, diluent or adjuvant, at least one neuroleptic compound in an amount effective to exert a neuroleptic effect in a patient requiring such treatment, and melatonin in an amount effective to ameliorate or prevent symptoms of tardive dyskensia developing in the patient.

2. A pharmaceutical formulation according to claim 1, which is additionally characterized by at least one of the following features:
(i) It is adapted for oral, rectal, parenteral or transdermal administration;
(ii) it is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 2.5-20 mg;
(iii) it is in the form of a controlled release formulation, wherein the melatonin is preferably released at a predetermined controlled rate;
(iv) it comprises also at least one melatonin receptor modifier and/or melatonin profile modifier;
(v) said neuroleptic compound is selected from compounds containing at least one of the following ring systems, namely, piperidine, pirperazine, morpholine, 5,6,7,8-tetrahydroindole, phenothiazine and thioxanthene.

3. A pharmaceutical formulation according to either claim 1 or claim 2, wherein said neuroleptic compound is selected from among chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, thiothixene, haloperidol, loxapine, molindone, clothiapine, clozapine, olanzapine, risperidone and zuclopenthixol acetate, and pharmaceutically acceptable salts thereof.

4. Use of melatonin in the manufacture of a medicament for the prevention or treatment of symptoms of tardive dyskensia in a patient.

5. Use according to claim 4, wherein said medicament takes the form of a pharmaceutical formulation, which includes at least one of the following additional components (a) and (b): (a) at least one carrier, diluent or adjuvant. (b) at least

one neuroleptic compound in an amount effective to exert a neuroleptic effect in a patient requiring such treatment.

6. Use according to claim 5, wherein said pharmaceutical formulation is additionally characterized by at least one of the following features:
(i) It is adapted for oral, rectal, parenteral or transdermal administration;
(ii) it is in unit dosage form, each unit dosage comprising an amount of melatonin which lies within the range of 2.5-20 mg;
(iii) it is in the form of a controlled release formulation, wherein the melatonin is preferably released at a predetermined controlled rate;
(iv) it comprises also at least one melatonin receptor modifier and/or melatonin profile modifier;
(v) said neuroleptic compound is selected from compounds containing at least one of the following ring systems, namely, piperidine, pirperazine, morpholine, 5,6,7,8-tetrahydroindole, phenothiazine and thioxanthene.

7. Use according to either claim 5 or claim 6, wherein said neuroleptic compound is selected from among chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, thiothixene, haloperidol, loxapine, molindone, clothiapine, clozapine, olanzapine, risperidone and zuclopenthixol acetate, and pharmaceutically acceptable salts thereof.