Description

It is known that the symptoms of depression can be eliminated by a d-phenylalanine treatment in 60 to 70% of the cases [Fischer et al.: Arzneim, Forsch. *25*, 132 (1975); Spatz et al.: Biol. Psychiat, *10*, 235238 (1975)], while d'l-phenylalanine when administered in a daily dose of at most 200 mg, is effective in 60% of the cases [Beckmann et al.: J. neural Transm, *41*, 123—134 (1977)]. During the treatment of parkinsonian patients with 1-phenylalanine infusion it has been observed that dysophoria, which is a concomitant phenomenon of Parkinson's disease, is decreased [Birkmayer: Wiener Zeitsch. für Nervenheilkunde *13*, 128—139 (19666].

In earlier open clinical tests [Varga and Tringer: Acta med. Acad. Sci. Hung. *23* 289—295 (1967)] a substantial improvement was achieved in depression clinical pictures by the administration of (+)-deprenyl [i.e. N - 1 - phenylisopropyl) - N - methyl - N - propinylamine.HCl] in daily doses of 50 to 100 mg.

(−)-Deprenyl is a potent specific monoaminoxydase B enzyme inhibiting compound, while the (+)-isomer primarily has an amphetamine activity and is essentially responsible for the antidepressive effect of the racemate reported in early publications.

The antidepressive activity of (−)-deprenyl has been examined by many authors. Mann et al. [Life Sci. *26*, 877—882 (1980); J. Clinn. Psychopharm, *2*, 54—57 (1982)] found an antidepressive activity at daily doses of 15 mg and 20 mg, respectively. Mendlewicz et al. [J. neural. Transm. *43*, 279—286 (1978); J. Affective Disorders *2*, 137—146 (1980)] administered the same compound in a daily dose of 15 mg, in combination with 3×300 mg of 5-OH-tryptophan and 3×75 mg of benzerazide and observed antidepressive activity, just like Liebowitz et al. (International Jumex Conference, May 5—8, 1982 Szombathely) who administered (−)-deprenyl in a daily dose of 30 mg. Others, such as Mendis et al. [Psychopharmacology *73*, 87—90 (1981)] did not find a better antidepressive activity than in case of placebo, when the compound was administered in a daily dose of 20 mg.

We have found that at a simultaneous administration of 1-phenylalanine (200—300 mg, preferably 250 mg, daily) and (−)-deprenyl employed in the selective monoaminoxydase B enzyme inhibiting range (3—10 mg, preferably 5—10 mg, daily) and optionally carbidopa [i.e. 3 - (3,4 - dihydroxyphenyl) - 2 - hydrazino - 2 - methyl - propionic acid monohydrate] in a daily dose of 20—30 mg or benzerazide [i.e. N - (DL-seryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazine] in a daily dose of 50—70 mg there can be observed a substantial increase of therapeutic antidepressive activity.

Test methods

Ambulant treatment: In this group 102 (44 male and 58 female) patients suffering from unipolar, chronic depression of 3 to 15 years were treated. The patients have got over at least five depressive phases and the antidepressant treatments employed earlier proved ineffective for the treatment of their disease. A combination of 250 mg of 1-phenylalanine and 5—10 mg of (−)-deprenyl was administered orally, in a single dose each morning, for 28 to 96 subsequent days.

Treatment of inpatients: In this group 53 (23 male and 30 female) patients suffering from grave, unipolar, chronic depression for 3 to 15 years were treated. The patients had at least five depressive phases and the conventional antidepressant treatments they had got earlier were ineffective also in their case. A combination of 250 mg of 1-phenylalanine and 10 mg of (−)-deprenyl was administered intravenously, in a single dose each morning, for 14 to 28 subsequent days.

The symptoms of depression were evaluated quantitatively on the basis of a scale widely used in the international literature. [Hamilton: J. Neurol. Neurosurg. Psychiat, *23*, 56—61 (1960)], by our own method [Birkmayer et al.: In: Masked Depression, Kielholz, P., ed., H. Huber Verlag, Bern-Stuttgart-Wien (1973)] and by the method of clinical, global estimation.

The explanation of the potent synergistic activity of the combined treatment is that 1-phenylalanine as a precursor and (−)-deprenyl by its selective monaminoxydase B enzyme inhibiting and uptake inhibiting activity regulate the level of cerebral amines in that way that the two effects of similar directions mutually potentiate each other.

The results are set forth in Table 1 below:

TABLE 1

Oral and intravenous treatment of unipolar depression with 1-phenylalanine and (−)-deprenyl

Parameters of treatment	oral treatment	intravenous treatment
Duration of depression (years)	3—15	3—15
Duration of combined treatment (days)	28—96	14—23 14—28
l-phenylalanine dose (mg/day)	250	250
(−)-deprenyl dose (mg/day)	5—10	10
Result of treatment		
First signs of improvement (after...weeks)	1 to 3	1 to 3
Improvement/recovery in % of total number of patients		
Cured	68.5	69.5
Improved	21.5	11.0
No improvement	6.0	12.0
Not evaluated	4.0	7.5

The evaluation has been carried out by the method disclosed in the Birkmayer et al reference cited (hereinabove (see the description of the test method). The average age of patients was 45 years (18—80), in both groups 60% of patients were women. The conventional antidepressive treatments were unsuccessful at these patients.

In the synergistic pharmaceutical compositions according to the invention the weight ratio of the components can be varied within a wide range. Generally 10—70 parts by weight, preferably 25 to 50 parts by weight of 1-phenyl-alanine are employed per 1 part by weight of (−)-deprenyl. The benzerazide component is used in an amount of 5 to 12 parts by weight, the carbidopa in an amount of 2 to 6 parts by weight related to (−)-deprenyl.

According to the invention the new synergistic compositions for the treatment of depressive symptoms may be transformed into conventional pharmaceutical compositions suitable for oral, parenteral or intravenous administration. The formulations are preferably prepared in the form of tablets, coated tablets, dragées, capsules or injectable preparations by conventional techniques used for the preparation of pharmaceutical compositions.

The tablets or injectable preparations according to the invention preferably contain 250 mg of 1-phenylalanine and 5 to 10 mg of (−)-deprenyl.

Further details of the invention are illustrated by the following non-limiting Examples.

Example 1

Dragée core

(−)-deprenyl hydrochloride	5.0 mg
1-phenylalanine	187.5 mg
Lactose	115.0 mg
Starch	15.5 mg
Polyvidone	20.0 mg
Magnesium stearate	7.0 mg
	350.0 mg

Coating

Luviscol® VA 64	13.0 mg
Talc	10.0 mg
Titanium dioxide	20.0 mg
Carbowax® 6000	7.0 mg
	50.0 mg

Example 2

Dragée core

(−)-deprenyl hydrochloride	5.0 mg
1-phenylalanine	50.0 mg
Lactose	70.0 mg
Starch	9.5 mg
Polyvidone	12.5 mg
Magnesium stearate	3.0 mg
	150.0 mg

Coating

Methocel® 60 Hg 15 cP	8.0 mg
Talc	6.0 mg
Titanium dioxide	12.0 mg
Carbowax® 6000	4.0 mg
	30.0 mg

Example 3

Dragée core

(−)-deprenyl	5.0 mg
1-phenylalanine	250.0 mg
Lactose	92.5 mg
Starch	19.0 mg
Polyvidone	25.5 mg
Magnesium stearate	8.0 mg
	400.0 mg

Coating

Luviscol® VA 64	6.5 mg
Methocel® 60 Hg 16 cP	6.5 mg
Talc	10.0 mg
Titanium dioxide	22.0 mg
Carbowax® 6000	5.0 mg
	50.0 mg

Preparation:

The components according to the above Examples are weighed separately in amounts required for the preparation of 10,000 dragée cores. The two active ingredients are homogenized with the total amount of lactose. Polyvidone is dissolved in 96% ethanol with slight heating. The hoomogenizate of the active ingredients and lactose is kneaded thoroughly and homogenized with the above granulating solution, in a suitable equipment. The granulate is dried at a temperature up to 35°C until the required degree of humidity is achieved, and is then regranulated. To the granulate obtained starch is added, and biconvex dragée cores are pressed weighing 150, 350 and 400 mg, respectively. The coating suspension is prepared by homogenizing the components of the coating, and subsequently dissolving the mixture obtained in isopropanol. The coating is applied to the spinned dragée cores by pneumatic sprayer. The coating is dried by an air stream of 35°C. The dragées are polished with a 1:1 mixture of isopropanol and water, containing 10% of Carbowax®, and packed in a conventional manner.

Example 4

(−)-deprenyl hydrochloride	5.0 mg
1-phenylalanine	250.0 mg
Carbidopa (equivalent to 25.0 mg of carbidopa anhydrate)	27.0 mg
Lactose	25.5 mg
Starch	14.5 mg
Polyvidone	20.0 mg
Magnesium stearate	8.0 mg
	350.0 mg

Example 5

(−)-deprenyl hydrochloride	5.0 mg
1-phenylalanine	250.0 mg
Benzerazide hydrochloride (corresponding to 62.5 mg of benzerazide)	71.25 mg
Lactose	23.75 mg
Starch	22.0 mg
Polyvidone	20.0 mg
Magnesium stearate	8.0 mg
	400.0 mg

Preparation of the above combinations:

From the components granulate is prepared as described in Examples 1 to 3, which is then filled into capsules of appropriate size in a suitable equuipment, and packed in a known manner.

Claims

1. Synergistic pharmaceutical compositions for the treatments of depressive symptoms comprising as active ingredient a combination of 1-phenylalanine and (−)-deprenyl [i.e. (−) - N - (1 - phenylisopropyl) - N - methyl - N - propinylamine hydrochloride] and optionally carbidopa [3 - (3,4 - dihydroxyphenyl) - 2 - hydrazino - 2 - methyl - propionic acid monohydrate] or benzerazide [i.e. N - (DL - seryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazine] in association with conventional inert, non-toxic solid or liquid pharmaceutical carriers.

2. A composition as claimed in claim 1, which comprises 10 to 70 parts by weight, preferably 25 to 50 parts by weight of 1-phenylalanine, optionally 5 to 12 parts by weight of benzerazide or 2 to 6 parts by weight of carbidopa related to 1 part by weight of (−)-deprenyl.

3. A composition as claimed in claim 1 or claim 2, in a form suitable for oral, parenteral or intravenous administration, preferably in the form of tablets, coated tablets, dragées, capsules or inectable preparations.

4. A composition as claimed in claim 3, in which a tablet contains 250 mg of 1-phenylalanine and 5 to 10 mg of (−)-deprenyl.

5. A composition as claimed in claim 3, in which an injection preparation contains 250 mg of 1-phenylalanine and 5 to 10 mg of (−)-deprenyl.

6. A process for the preparation of synergistic pharmaceutical compositions, which comprises admixing as active ingredient a combination of 1-phenylalanine and (−)-deprenyl [(−) - N - (1 - phenylisopropyl) - N - methyl - N - propinylamine hydrochloride] and optionally carbidopa [3 - (3,4 - dihydroxyphenyl) - 2 - hydrazino - 2 - methyl - propionic acid monohydrate) or benzerazide [N - (DL - seryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazine] with conventional inert, non-toxic solid or liquid pharmaceutical carriers.

7. A process as claimed in claim 6, which comprises using 10 to 70 parts by weight, preferably 25 to 50 parts by weight of 1-phenylalanine and optionally 5 to 12 parts by weight of benzerazide or 2 to 6 parts by weight of carbidopa related to 1 part by weight of (−)-deprenyl.

8. The use of a combination of 1-phenylalanine and (−)-deprenyl and optionally carbidopa or benzerazide in the manufacture of pharmaceutical compositions for the treatment of depressive symptoms.

Patentansprüche

1. Synergistische pharmazeutische Kompositionen für die Behandlung von Depressions-symptomen, die als aktives Ingrediens eine Kombination von 1-Phenylalanin und (−)-Deprenyl [d.h. (−) - N - (1 - Phenyl - isopropyl) - N - methyl - N - propinylamin - Hydrochlorid] und gewünschtenfalls Carbidopa [3 - 3,4 - Dihydroxyphenyl) - 2 - hydrazino - 2 - methyl - propionsäure - Monohydrat] oder Benzerazid [d.h. N - (DL - Seryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazin] sowie konventionelle, inerte, nicht-toxische feste üder flüssige pharmazeutische Trägermaterialien enthalten.

2. Komposition gemäß Anspruch 1, gekennzeichnet durch einen Gehalt an 10 bis 70 Gewt., vorzugsweise 25 bis 50 Gewt., 1-Phenylalanin und gewünschtenfalls 5 bis 12 Gewt. Benzerazid oder 2 bis 6 Gewt. Carbidopa-auf 1 Gewt. (−)-Deprenyl bezogen.

3. Komposition gemäß Anspruch 1 oder 2, in einer für die orale, parenterale oder intravenöse

Example 5

(−)-deprenyl hydrochloride	5.0 mg
1-phenylalanine	250.0 mg
Benzerazide hydrochloride (corresponding to 62.5 mg of benzerazide)	71.25 mg
Lactose	23.75 mg
Starch	22.0 mg
Polyvidone	20.0 mg
Magnesium stearate	8.0 mg
	400.0 mg

Preparation of the above combinations:

From the components granulate is prepared as described in Examples 1 to 3, which is then filled into capsules of appropriate size in a suitable equupment, and packed in a known manner.

Claims

1. Synergistic pharmaceutical compositions for the treatments of depressive symptoms comprising as active ingredient a combination of 1-phenylalanine and (−)-deprenyl [i.e. (−) - N - (1 - phenylisopropyl) - N - methyl - N - propinylamine hydrochloride] and optionally carbidopa [3 - (3,4 - dihydroxyphenyl) - 2 - hydrazino - 2 - methyl - propionic acid monohydrate] or benzerazide [i.e. N - (DL - seryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazine] in association with conventional inert, non-toxic solid or liquid pharmaceutical carriers.

2. A composition as claimed in claim 1, which comprises 10 to 70 parts by weight, preferably 25 to 50 parts by weight of 1-phenylalanine, optionally 5 to 12 parts by weight of benzerazide or 2 to 6 parts by weight of carbidopa related to 1 part by weight of (−)-deprenyl.

3. A composition as claimed in claim 1 or claim 2, in a form suitable for oral, parenteral or intravenous administration, preferably in the form of tablets, coated tablets, dragées, capsules or inectable preparations.

4. A composition as claimed in claim 3, in which a tablet contains 250 mg of 1-phenylalanine and 5 to 10 mg of (−)-deprenyl.

5. A composition as claimed in claim 3, in which an injection preparation contains 250 mg of 1-phenylalanine and 5 to 10 mg of (−)-deprenyl.

6. A process for the preparation of synergistic pharmaceutical compositions, which comprises admixing as active ingredient a combination of 1-phenylalanine and (−)-deprenyl [(−) - N - (1 - phenylisopropyl) - N - methyl - N - propinylamine hydrochloride] and optionally carbidopa [3 - (3,4 - dihydroxyphenyl) - 2 - hydrazino - 2 - methyl - propionic acid monohydrate) or benzerazide [N - (DL - seryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazine] with conventional inert, non-toxic solid or liquid pharmaceutical carriers.

7. A process as claimed in claim 6, which comprises using 10 to 70 parts by weight, preferably 25 to 50 parts by weight of 1-phenylalanine and optionally 5 to 12 parts by weight of benzerazide or 2 to 6 parts by weight of carbidopa related to 1 part by weight of (−)-deprenyl.

8. The use of a combination of 1-phenylalanine and (−)-deprenyl and optionally carbidopa or benzerazide in the manufacture of pharmaceutical compositions for the treatment of depressive symptoms.

Patentansprüche

1. Synergistische pharmazeutische Kompositionen für die Behandlung von Depressions-symptomen, die als aktives Ingrediens eine Kombination von 1-Phenylalanin und (−)-Deprenyl [d.h. (−) - N - (1 - Phenyl - isopropyl) - N - methyl - N - propinylamin - Hydrochlorid] und gewünschtenfalls Carbidopa [3 - 3,4 - Dihydroxyphenyl) - 2 - hydrazino - 2 - methyl - propionsäure - Monohydrat] oder Benzerazid [d.h. N - (DL - Seryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazin] sowie konventionelle, inerte, nicht-toxische feste üder flüssige pharmazeutische Trägermaterialien enthalten.

2. Komposition gemäß Anspruch 1, gekennzeichnet durch einen Gehalt an 10 bis 70 Gewt., vorzugsweise 25 bis 50 Gewt., 1-Phenylalanin und gewünschtenfalls 5 bis 12 Gewt. Benzerazid oder 2 bis 6 Gewt. Carbidopa-auf 1 Gewt. (−)-Deprenyl bezogen.

3. Komposition gemäß Anspruch 1 oder 2, in einer für die orale, parenterale oder intravenöse

Verabreichung geeigneten Form, vorzugsweise in Form von Tabletten, überzogenen Tabletten, Dragées, Kapseln oder injizierbaren Präparaten.

4. Komposition gemäß Anspruch 3, in Form von 250 mg 1-Phenylalanin und 5 bis 10 mg (−)-Deprenyl enthaltenden Tabletten.

5. Komposition gemäß Anspruch 3 in Form von 250 mg 1-Phenylalanin und 5 bis 10 mg (−)-Deprenyl enthaltenden Injektions-präparaten.

6. Verfahren zur Herstellung synergistischer pharamazeutischer Kompositionen, dadurch gekennzeichnet, daß man als aktives Ingrediens eine Kombination von 1-Phenylalanin und (−)-Deprenyl [(−) - N - (1 - Phenyl - isopropyl) - N - methyl - N - propinylamin - Hydrochlorid] und gewünschtenfalls Carbidopa [3 - (3,4 - Dihydroxyphenyl) - 2 - hydrazino - 2 - methyl - propionsäure-Monohydrat] oder Benzerazid [N - (DL - Seryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazin] mit konventionellen inerten, nicht-toxischen festen oder flüssigen pharmazeutischen Trägermaterialien vermischt.

7. Verfahren gemäß Anspruch 6, gekennzeichnet durch die Verwendung von 10 bis 70 Gewt., vorzugsweise 25 bis 50 Gew., 1-Phenylalanin und gewünschtenfalls 5 bis 12 Gewt. Benzerazid oder 2 bis 6 Gewt. Carbidopa-auf 1 Gewt. (−)-Deprenyl bezogen.

8. Verwendung einer Kombination von 1-Phenylalanin und (−)-Deprenyl und gewünschtenfalls Carbidopa oder Benzerazid zur Herstellung von pharmazeutischen Kompositionen für die Behandlung von Depressions-symptomen.

Revendications

1. Compositions pharmaceutiques synergiques pour le traitement des symptômes dépressifs comprenant comme ingrédient actif une combinaison de 1-phénylalanine et de (−)-déprényl [c'est-à-dire chlorhydrate de (−) - N - (1 - phénylisopropyl) - N - méthyl - N - propinylamine] et éventuellement de carbidopa [acide 3 - (3,4 - dihydroxyphényl) - 2 - hydrazino - 2 - méthylpropionique monohydraté] ou de benzérazide [c'est-à-dire N - (DL - séryl) - N' - (2,3,4 - trihydroxybenzyl)hydrazine] en association avec des supports pharmaceutiques inertes classiques, non oxiques, solides ou liquides.

2. Composition selon la revendication 1, qui comprend de 10 à 70 parties en poids, de préférence de 25 à 50 parties en poids de 1-phénylalanine, éventuellement de 5 à 12 parties en poids de benzérazide ou de 2 à 6 parties en poids de carbidopa pour 1 partie en poids de (−)-déprényle.

3. Composition selon la revendication 1 ou la revendication 2, sous une forme appropriée à l'administration orale, parentérale ou intraveineuse, de préférence sous forme de comprimés, comprimés enrobés, dragées, capsules ou préparations injectables.

4. Composition selon la revendication 3, dans laquelle un comprimé contient 250 mg de 1-phénylalanine et de 5 à 10 mg de (−)-déprényle.

5. Composition selon la revendication 3, dans laquelle une préparation injectable contient 250 mg de 1-phéhylalanine et de 5 à 10 mg de (−)-déprényle.

6. Procédé de préparation de compositions pharmaceutiques synergiques, dans lequel on mélange comme ingrédient actif une combinaison de 1-phénylalanine et de (−)-déprényle [chlorhydrate de (−) - N - (1 - phénylisopropyl) - N - méthyl - N - propinylamine] et éventuellement de carbidopa [acide 3 - (3,4 - dihydroxyphényl) - 2 - hydrazino - 2 - méthyl - propionique monohydraté)] ou de benzérazide [N - (DL - séryl) - N' - (2,3,4 - trihydroxybenzyl) - hydrazine] avec des supports pharmaceutiques inertes classiques, non toxiques, solides ou liquides.

7. Procédé selon la revendication 6, dans lequel on utilise de 10 à 70 parties en poids, de préférence de 25 à 50 parties en poids, de 1-phénylalanine et éventuellement de 5 à 12 parties en poids de benzérazide ou de 2 à 6 parties en poids de carbidopa pour 1 partie en poids de (−)-déprényle.

8. Application d'une combinaison de 1-phénylalanine et de (−)-déprényle et éventuellement de carbidopa ou de benzérazide à la préparation de compositions pharmaceutiques pour le traitement des symptômes dépressifs.