Drugs of the Future 2001, 26(3): 219-223

CCC: 0377-8282/2001

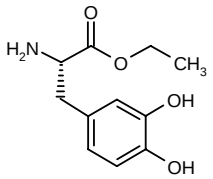
Etilevodopa

Prop INN

Antiparkinsonian
Dopamine Precursor

Levodopa Ethyl Ester
TV-1203

2(*S*)-Amino-3-(3,4-dihydroxyphenyl)propionic acid ethyl ester



$C_{11}H1_5NO_4$ Mol wt: 225.2425

CAS: 037178-37-3

EN: 134939

Synthesis

Etilevodopa has been obtained by several different methods: (i) esterification of 3-hydroxy-L-tyrosine (I) (L-DOPA) with ethanol catalyzed by dry HCl gas (1); (ii) esterification of 3-hydroxy-L-tyrosine (I) (L-DOPA) by means of $SOCl_2$ in hot ethanol (2); (iii) enzymatic hydroxylation of L-tyrosine ethyl ester (II) by means of mushroom tyrosinase in a phosphate buffer (3). Scheme 1.

Introduction

Parkinson's disease is a progressive neurodegenerative disease that affects 1-1.5 million Americans. It is estimated that 1-2 individuals suffer from the disorder for every 1000 worldwide. The predominant pathological feature of Parkinson's disease is dopaminergic neuronal cell death in the substantia nigra and degeneration of the nigrostriatal pathway resulting in the gradual loss of the ability to control muscles. The disease presents with bradykinesia, rigidity, tremor at rest and postural instability (4).

Although Parkinson's disease is, as of yet, incurable, there are agents available which provide alleviation of symptoms and a slowing of disease progression. The result can be near normal life expectancy and satisfactory quality of life for patients. The most common pharmacological treatment to control symptoms of the disease involves administration of dopaminergic compounds, including dopamine precursors. Levodopa (L-DOPA; L-3,4-dihydroxyphenylalanine) is the immediate biological precursor of dopamine and is the mainstay for treatment of Parkinson's disease. L-DOPA is usually used in combination with other agents to control specific symptoms and/or to enhance L-DOPA activity (4). However, L-DOPA has a number of disadvantages. It is not soluble in water and is easily metabolized either via oxidation or peripheral decarboxylation. The consequence following oral administration is that only approximately 1% of the dose reaches the CNS. To counteract these disadvantages, high L-DOPA doses have been employed. However, although substantial benefits are seen in the early stages of the disease, most patients become disabled from the adverse effects particularly motor response complications and decreasing duration of response to the agents. Those patients suffering erratic responses to L-DOPA due to variable absorption of the agent are referred to as fluctuators (4, 5).

Researchers have focused their efforts on improving drugs that act on the dopaminergic system. Agents under development for Parkinson's disease are shown in Table I. The search continues for agents that penetrate into the brain rapidly and are subsequently slowly metabolized. These agents must also possess a good safety profile. The development of prodrugs which would be more water and/or lipid soluble is an option for optimizing the effects of L-DOPA. A series of L-DOPA ester derivatives were synthesized which appear to be at least as effective as L-DOPA (6-10). Of these compounds, L-DOPA ethyl ester, etilevodopa, a stable, highly soluble prodrug, has been shown to be clinically more effective than L-DOPA as a treatment for Parkinson's disease and has been chosen for further development.

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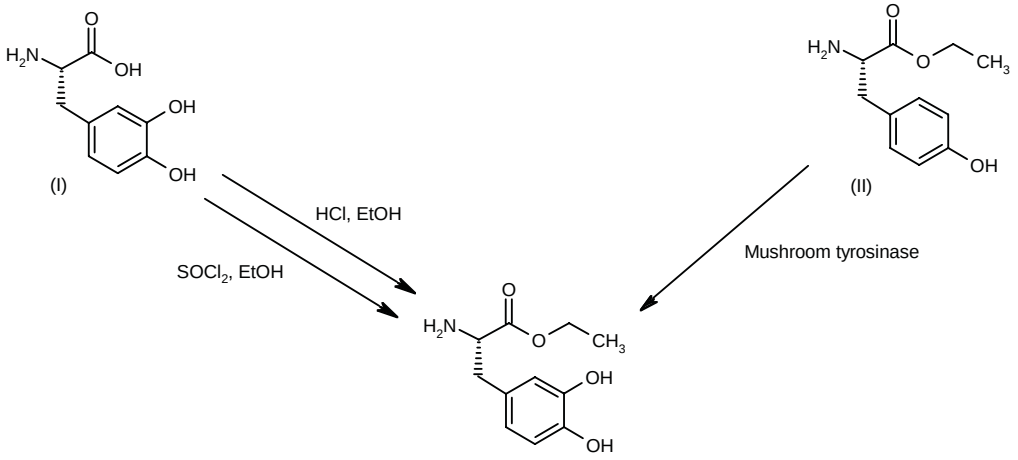
Scheme 1: Synthesis of Etilevodopa



Pharmacological Actions

An *in vitro* study using excised intestines and stomachs from rats and artificial pig pancreatic extract demonstrated that etilevodopa was rapidly hydrolyzed to L-DOPA in the duodenum and artificial pig pancreatic extract (> 80%) but not in the stomach. *In vivo* experiments performed in rats administered etilevodopa orally demonstrated rapid absorption of L-DOPA into the portal vein and abdominal artery. Maximal L-DOPA plasma concentrations were achieved in 7-8 min postdosing while plasma levels of etilevodopa were negligible. These results indicate that the prodrug was completely hydrolyzed in the gastrointestinal tract (11).

The effects of etilevodopa on dopamine metabolism in the striatum were examined in rats following s.c. and i.p. administration of the agent alone (325 mg/kg) or in combination (65 mg/kg) with carbidopa (10 mg/kg s.c. or i.p. 1 h before etilevodopa). Treatment with etilevodopa alone resulted in elevations in striatal L-DOPA, dopamine and the dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC); plasma concentrations were maximal at 0.5-1 h postdosing and levels were similar to those observed after treatment with L-DOPA (250 mg/kg i.p.). Administration of etilevodopa s.c. produced greater elevations that were sustained longer as compared to i.p. administration. Combination etilevodopa/carbidopa also significantly increased striatal levels of L-DOPA and dopamine, with elevations observed as early as 5 and 10 min postdosing, respectively (12).

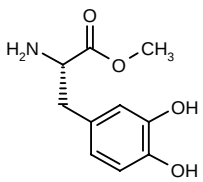
Further studies *in vivo* using rats with unilateral 6-hydroxydopamine (6-OHDA; 8 and 4 μg injected into the right anteromedial substantia nigra and right forebrain bundle, respectively)-induced nigral lesions demonstrated that treatment with etilevodopa (25 or 50 mg/kg s.c.) produced similar contraversive circling responses as L-DOPA. Similar circling responses were also observed in rats pretreated with carbidopa (10 mg/kg i.p. 45 min before etilevodopa). These results suggest that etilevodopa may be effective as a rescue therapy for parkinsonian patients with response fluctuations during "off" situations (12).

Clinical Studies

An open trial conducted in 7 fluctuating patients with advanced idiopathic Parkinson's disease (mean disease duration of 12.2 ± 4.1 years; mean duration of fluctuations of 5.7 ± 2.5 years) showed the efficacy of etilevodopa (150-400 mg s.c. or i.m. 4 injections/day for 2 days given when patients were in "off" periods) as a rescue therapy for response fluctuations; patients also received carbidopa (25 mg p.o.) 1 h before etilevodopa. Following s.c. and i.m. administration of etilevodopa, 96.5 and 93%, respectively, of the injections resulted in successes in turning the patients "on". No differences in the mean latency to an "on" period were observed in groups administered the agent s.c. or i.m. although latencies were shorter and durations of "on" time were longer (35, 112, 146 and 200 min in the a.m. following s.c. injections of 150, 200, 250 and 300 mg, respectively) with higher doses. Etilevodopa injections produced rapid and sustained increases in plasma L-DOPA and the prodrug was not detected in plasma following dosing. Treatment was well tolerated with only minor adverse events experienced. These included occasional and transient local erythema and induration at injection site, vertigo, light-headedness and sweating. No patients discontinued due to adverse effects. However, 2 patients receiving 250 mg

Table I: Drugs acting on the dopaminergic system under development for Parkinsons' disease (Prous Science R&D Backgrounders database).

Drug Name	Company	Mechanism of Action	Status
1. Melevodopa HCl (*Levomet*)	Chiesi	Dopamine precursor	Launched 2000
2. Apomorphine HCl	Pentech	Dopamine D_2 agonist (high-dose sublingual tablets)	Phase III
3. DU-127090*	Solvay	Dopamine D_2 partial agonist/antagonist and 5-HT_{1A} agonist	Phase III
4. Etilevodopa	Teva/Lundbeck	Dopamine precursor	Phase III
5. ABT-431	Abbott	Dopamine D_1 agonist	Phase II
6. Brasofensine sulfate	NeuroSearch	Dopamine reuptake inhibitor	Phase II
7. BTS-74398	Knoll/DevCo	Monoamine reuptake inhibitor	Phase II
8. PNU-95666A	Pharmacia	Dopamine D_2 agonist	Phase II
9. Rotigotine HCl	Discovery Therapeutics/Schwarz	Dopamine D_2 agonist (transdermal patch)	Phase II
10. SLV-308	Solvay	Partial dopamine D_2 agonist/5-HT_{1A} agonist	Phase II
11. *Zydis* apomorphine	Orion	Dopamine D_2 agonist (fast-dissolving oral formulation)	Clinical Trials
12. CGP-3466	Novartis	Inhibitor of dopaminergic neuronal degeneration	Preclinical
13. GMC-1111	Pharmacia/Pfizer	Dopamine D_2 agonist/dopamine D_3 antagonist	Preclinical
14. O-1369*	Boston Life Sciences	Dopamine reuptake inhibitor	Preclinical
15. OSU-6162	Pharmacia	Dopamine D_2 receptor ligand	Preclinical
16. S-32504*	Servier	Dopamine D_3 agonist	Preclinical
17. SPD-451*	CeNeS/Shire	Dopamine D_1 agonist	Preclinical



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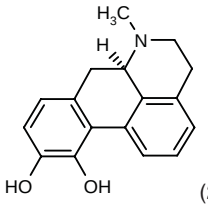

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.H2O

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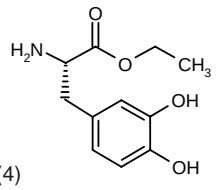

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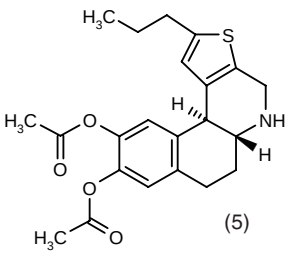

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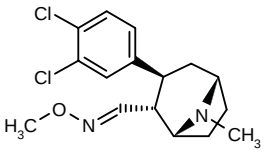

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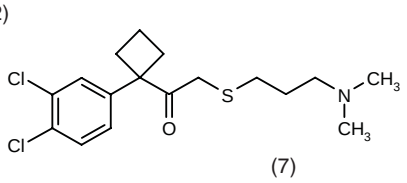

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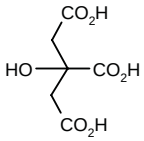

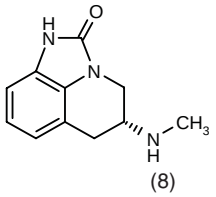

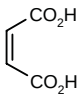

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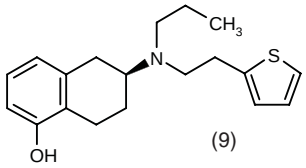

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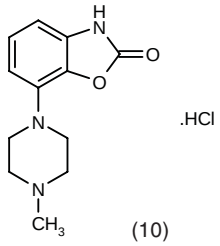

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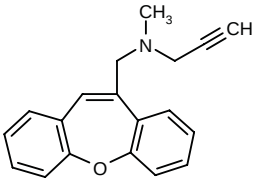

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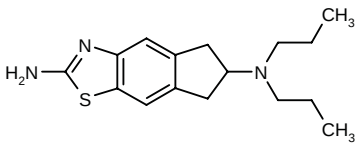

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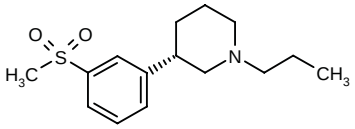

(15)

*Structure not yet detected.

Box 1: Efficacy of etilevodopa as rescue therapy in patients with Parkinson's disease (13) [Prous Science CSline database].

Design	Open, crossover clinical study
Population	Patients with advanced idiopathic fluctuating Parkinson's disease (n = 7)
Treatments	Levodopa, 857 mg [mean] [given in 4-10 divided doses] + Carbidopa, 25 mg p.o. → Etilevodopa, 150-400 mg s.c. (or i.m.) x 6.4 doses [mean] + Carbidopa, 25 mg p.o.
Results	Rate of s.c. patients with clinical benefit (turning on) (%): E (96.5) Rate of i.m. patients with clinical benefit (turning on) (%): E (93) Time (latency) to "on" (min): E150 (50) > E300 (25) Duration of the "on" response (min): E300 (225) > E150 (50)
Conclusions	Etilevodopa was well tolerated and effective in Parkinson's disease patients in disabling "off" situations

Box 2: Efficacy of etilevodopa as rescue therapy in patients with Parkinson's disease (14) [Prous Science CSline database].

Design	Open clinical study
Population	Patients with Parkinson's disease with response fluctuations on levodopa/carbidopa (n = 8)
Treatments	Carbidopa, 25 mg p.o. + Etilevodopa, 150-300 mg [escalating doses] b.i.d. s.c.
Results	Patients (%) turning "on": LE+C (100) Mean time to "on": L/C > LE/C Mean "on" duration: LE+C > L/C
Conclusions	Etilevodopa was effective in fluctuating Parkinson's disease

Box 3: Efficacy of etilevodopa vs. levodopa plus carbidopa in patients with Parkinson's disease (15) [Prous Science CSline database].

Design	Open clinical study
Population	Patients with Parkinson's disease with response fluctuations (n = 11)
Treatments	Levodopa/Carbidopa → Carbidopa, 25 mg p.o. + Etilevodopa, 150-300 mg [escalating doses] b.i.d. s.c. or i.m.
Results	Mean time to "on": E+C > L/C Mean "on" duration: E+C > L/C
Conclusions	Etilevodopa was effective in fluctuating Parkinson's disease

Box 4: Efficacy of levodopa ethylester vs. crushed levodopa in patients with Parkinson's disease (16) [Prous Science CSline database].

Design	Comparative, randomized, double-blind, crossover clinical study
Population	Patients with Parkinson's disease and "delayed-on" and "no-on" phenomena (n = 11)
Treatments	Crushed levodopa + Carbidopa p.o. Etilevodopa p.o.
Results	Mean time to "on" (min): L+C (45.3) > E (31.5) Mean "on" duration (min): E (448) > L+C (406) Rate of patients with "no-on" phenomena: E = L+C
Conclusions	Etilevodopa may be more effective than crushed levodopa plus carbidopa in fluctuating Parkinson's disease

s.c. and i.m., respectively, did not show any clinical benefits following etilevodopa treatment. In one patient, L-DOPA levels did not reach the threshold of the patient's "on" response (780 *vs.* 1816-2646 ng/ml) while in the other patient, plasma L-DOPA levels were only slightly lower than those observed at the onset of the patient's "on" period (2000 *vs.* 2169-3518 ng/ml) (13) (Box 1). Similar results were reported for 2 other trials involving 8 and 11 fluctuating parkinsonian patients, respectively, given etilevodopa (150-300 mg) s.c. or i.m. alone or 1 h before oral carbidopa (25 mg) (14, 15) (Boxes 2 and 3).

A randomized, double-blind, crossover trial comparing the efficacy of an oral etilevodopa solution and crushed tablets of L-DOPA/carbidopa in 11 patients with idiopathic Parkinson's disease with response fluctuations ("delayed-on" and "no-on" phenomena), showed that the oral etilevodopa solution was more convenient and slightly more effective than the crushed L-DOPA/carbidopa tablets. Etilevodopa treatment resulted in a shorter average mean time to "on" (31.5 ± 14.6 *vs.* 45.3 ± 29.9 min) and a longer mean "on" duration (448 ± 133 *vs.* 406 ± 194 min) during the entire day as compared to L-DOPA/carbidopa. No differences were observed in the proportion of "no-on" phenomena between the two treatments. Moreover, significantly higher plasma L-DOPA levels were achieved with etilevodopa treatment (29.7 ± 15.3 *vs.* 21.9 ± 8.5 ng/ml/mg) (16) (Box 4).

Etilevodopa is currently undergoing phase III trials as a treatment for Parkinson's disease (17, 18).

Manufacturer

Teva Pharmaceutical Industries Ltd. (IL); licensed to H. Lundbeck A/S (DK) for Europe.

References

1. Lidor, R., Bahar, E., Frenkel, A. (Teva Pharmaceutical Industries Ltd.; Teva Pharmaceuticals USA, Inc.). *Process for manufacture of L-DOPA ethyl ester.* WO 0027801.

2. Milman, I., Veinberg, A., Atlas, D., Melamed, E. (Yissum Research Development Co.; Teva Pharmaceutical Industries Ltd.). *Process for preparing ethyl ester of L-DOPA.* EP 0610595, US 5354885.

3. Ahmed, G., Vulfson, E.N. *Facile synthesis of L-dopa esters by the combined use of tyrosinase and α-chymotrypsin.* Biotechnol Lett 1994, 16: 367-72.

4. Prous Science R&D Backgrounders: *Parkinson's disease (online publication).* Updated February 13, 2001.

5. Mendis, T., Suchowersky, O., Lang, A., Gauthier, S. *Management of Parkinson's disease: A review of current and new therapies.* Can J Neurol Sci 1999, 26: 89-103.

6. Marrel, C., Boss, G., van de Waterbeemd, H., Testa, B., Cooper, D., Jenner, P., Marsden, C.D. *L-DOPA esters as potential prodrugs. Part I. Physicochemical properties.* Eur J Med Chem - Chim Ther 1985, 20: 459-65.

7. Marrel, C., Boss, G., Testa, B., van de Waterbeemd, H., Cooper, D., Jenner, P., Marsden, C.D. *L-DOPA esters as potential prodrugs. Part II. Chemical and enzymatic hydrolysis.* Eur J Med Chem - Chim Ther 1985, 20: 467-70.

8. Cooper, D.R., Marrel, C., van de Waterbeemd, H., Testa, B., Jenner, P., Marsden, C.D. *L-Dopa esters as potential prodrugs: Behavioural activity in experimental models of Parkinson's disease.* J Pharm Pharmacol 1987, 39: 627-35.

9. Cooper, D.R., Marrel, C., van de Waterbeemd, H., Testa, B., Jenner, P., Marsden, C.D. *L-Dopa esters as potential prodrugs: Effect on brain concentration of dopamine metabolites in reserpinized mice.* J Pharm Pharmacol 1987, 39: 809-18.

10. Brunner-Guenat, M., Carrupt, P.-A., Lisa, G., Testa, B., Rose, S., Thomas, K., Jenner, P., Ventura, P. *Esters of L-dopa: Structure-hydrolysis relationships and ability to induce circling behaviour in an experimental model of hemiparkinsonism.* J Pharm Pharmacol 1995, 47: 861-9.

11. Blaugrund, E., Myke, A., Sayag, N., Melamed, E. *Intestinal hydrolysis of TV-1203, a levodopa prodrug.* Parkinsonism Relat Disord 1999, 5(Suppl.): Abst P-TU-072.

12. Djaldetti, R., Atlas, D., Melamed, E. *Effect of subcutaneous administration of levodopa ethyl ester, a soluble prodrug of levodopa, on dopamine metabolism in rodent striatum: Implication for treatment of Parkinson's disease.* Clin Neuropharmacol 1996, 19: 65-71.

13. Djaldetti, R., Melamed, E. *Levodopa ethylester: A novel rescue therapy for response fluctuations in Parkinson's disease.* Ann Neurol 1996, 39: 400-4.

14. Djaldetti, R., Atlas, D., Melamed, E. *Subcutaneous injections of levodopa ethylester: A potential novel rescue therapy for response fluctuations in patients with Parkinson's disease.* Neurology 1995, 45(4, Suppl. 4): Abst 415S.

15. Djaldetti, R., Atlas, D., Melamed, E. *Levodopa ethylester: A novel therapeutic strategy for treatment of response fluctuations in patients with Parkinson's disease.* Ann Neurol 1995, 38(2): Abst T177.

16. Djaldetti, R., Ziv, I., Melamed, E. *Double-blind, crossover trial of oral levodopa ethylester vs. crushed levodopa for treatment of response fluctuations in Parkinson's disease.* Mov Disord 1996, 11(Suppl. 1): Abst P512.

17. *Teva finalizes separate agreements with Aventis and Lundbeck.* DailyDrugNews.com (Daily Essentials) February 16, 2001.

18. *Important advances in the Lundbeck pipeline during 2000.* DailyDrugNews.com (Daily Essentials) January 10, 2001.