

Dopamine Replacement

Laurie K Mischley, ND PhD MPH



PARKINSON'S SCHOOL

An Online Course for Patients and Providers

Drugs Classes in PD

- MAO-B Inhibitors
- Dopamine Agonists
- L-Dopa Supplementation +
Decarboxylase Inhibitor
(levodopa/ carbidopa)



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Monoamine Oxidase-B (MAO-B) Inhibitors

- Rasagiline
- Selegiline/ L-Deprenyl
- Safinamide



1978: Levodopa-Sparing Role for MAO-B Inhibitors

Experiences With L-Deprenyl in Parkinsonism

E. Csanda, J. Antal, M. Ant6ny, and A. Csanaky

Semmelweis University of Medicine, Department of Neurology, Budapest, Hungary

With 6 Figures

Received July 14, 1978

Summary

In about 2/3 of the cases studied (152 patients), the combination of deprenyl and the substitution-therapy has a favourable effect as it tends to normalize motor activity. Although the administering of deprenyl renders neither L-Dopa nor the decarboxylase inhibitor superfluous, their side effects can be slightly reduced as their dose is reduced. Therefore it is advised to give all patients a trial with this drug.



1989: Data Suggests Selegiline Slows PD Progression

N Engl J Med. 1989 Nov 16;321(20):1364-71.

Effect of deprenyl on the progression of disability in early Parkinson's disease.

Parkinson Study Group.

Abstract

In a clinical trial that is still in progress, we studied the ability of deprenyl and tocopherol, antioxidative agents that act through complementary mechanisms, to delay the onset of disability necessitating levodopa therapy (the primary end point) in patients with early, untreated Parkinson's disease. Eight hundred subjects were randomly assigned in a two-by-two factorial design to receive deprenyl, tocopherol, a combination of both drugs, or placebo, and were followed up to determine the frequency of development of the end point. The interim results of independent monitoring prompted a preliminary comparison of the 401 subjects assigned to tocopherol or placebo with the 399 subjects assigned to deprenyl, alone or with tocopherol. Only 97 subjects who received deprenyl reached the end point during an average 12 months of follow-up, as compared with 176 subjects who did not receive deprenyl (P less than 10(-8). The risk of reaching the end point was reduced by 57 percent for the subjects who received deprenyl (Cox hazard ratio, 0.43; 95 percent confidence limits, 0.33 and 0.55; P less than 10(-10). The subjects who received deprenyl also had a significant reduction in their risk of having to give up full-time employment ($P = 0.01$). We conclude from these preliminary results that the use of deprenyl (10 mg per day) delays the onset of disability associated with early, otherwise untreated cases of Parkinson's disease.

Comment in

Deprenyl for the treatment of early Parkinson's disease. [N Engl J Med. 1990]

PMID: 2509910 DOI: 10.1056/NEJM198911163212004

We conclude deprenyl (10 mg/day) delays the onset of disability with early, otherwise untreated cases of PD.



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1989: Data Suggests Selegiline Slows PD Progression

Science. 1989 Aug 4;245(4917):519-22.

The effect of deprenyl (selegiline) on the natural history of Parkinson's disease.

Tetrad JW¹, Langston JW.

Author information

¹ California Parkinson's Foundation, San Jose 95128.

Abstract

The effects of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a neurotoxin that produces the symptoms of Parkinson's disease, can be fully prevented in experimental animals by inhibiting monoamine oxidase B. On the basis of this observation, a double-blind, placebo-controlled study in patients with early Parkinson's disease was initiated to determine whether deprenyl (a selective monoamine oxidase B inhibitor) would delay the need for L-dopa therapy by slowing the progression of the disease. Fifty-four patients were randomly assigned to deprenyl (10 mg/day) or placebo treatment groups and followed until L-dopa therapy was indicated or until the patient had been in the study for 3 years. Analysis of Kaplan-Meier survival curves for each group showed that deprenyl delayed the need for L-dopa therapy; the average time until L-dopa was needed was 312.1 days for patients in the placebo group and 548.9 days for patients in the deprenyl group. Disease progression, as monitored by five different assessment scales, was slowed (by 40 to 83% per year) in the deprenyl group compared to placebo. Therefore, early deprenyl therapy delays the requirement for antiparkinsonian medication, possibly by slowing progression of the disease.

Comment in

Deprenyl and the progression of Parkinson's disease. [Science. 1990]

PMID: 2502843 DOI: 10.1126/science.2502843

Therefore, early deprenyl therapy delays the requirement for antiparkinsonian medications, possibly by slowing progression of the disease.



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Rasagiline Designed to Improve Upon Selegeline

Neuroreport. 2000 Dec 18;11(18):3937-41.

The neuronal survival effects of rasagiline and deprenyl on fetal human and rat ventral mesencephalic neurones in culture.

Goggi J¹, Theofilopoulos S, Riaz SS, Jauniaux E, Stern GM, Bradford HF.

 **Author information**

¹ Department of Biochemistry, Imperial College of Science, Technology and Medicine, South Kensington, London, UK.

Abstract

The neuronal survival properties of rasagiline (R(+)-N-propargyl-1-aminindane mesylate or TVP-1012), a novel monoamine oxidase B inhibitor, have been investigated using neuronal cell cultures from fetal rat and human ventral mesencephalon. The ability of rasagiline to reduce the rate of neuronal cell loss in vitro was tested using primary neuronal cell lines and immunohistochemistry to quantify the reduction in cell death. Direct comparison was made with deprenyl, a widely used and long established monoamine oxidase B inhibitor. Rasagiline was shown to act 15-20% more effectively as a neuronal survival agent than deprenyl, increasing both the survival of the total number of neurones and selectively increasing the survival of dopaminergic neurones with no statistically significant increase in survival of GABAergic neurones.

PMID: 11192605 DOI: 10.1097/00001756-200012180-00007

- “using neuronal cell cultures...rasagiline was show to act 15-20% more effectively as a neuronal survival agent than deprenyl...”
- Industry has little incentive for investing in research on generic medications, tried to make a new, improved version.



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Y2K: Enter Rasagiline

Clin Neuropharmacol. 2000 Nov-Dec;23(6):324-30.

Rasagiline mesylate, a new MAO-B inhibitor for the treatment of Parkinson's disease: a double-blind study as adjunctive therapy to levodopa.

Rabey JM¹, Sagi I, Huberman M, Melamed E, Korczyn A, Giladi N, Inzelberg R, Djaldetti R, Klein C, Bercz G: Rasagiline Study Group.

 **Author information**

¹ Department of Neurology, Assaf Harofeh Medical Center, Zerifin, Sackler Faculty of Medicine, Tel-Aviv University, Israel.

Abstract

Rasagiline mesylate (TVP-1012) is a potent, selective, non-reversible MAO-B inhibitor, without the tyramine-potentiating effect and with neuroprotective activities. The benefit of rasagiline as monotherapy in patients with early Parkinson's disease (PD) has already been reported. To evaluate the safety, tolerability, and clinical effect of rasagiline as adjunctive therapy to levodopa, a multicenter, double-blind, randomized, placebo-controlled, parallel-group study (0.5, 1, and 2 mg/d) was conducted for 12 weeks in 70 patients with PD (mean age, 57.4 y; mean disease duration, 5.7 y; 32 patients had motor fluctuations). A beneficial clinical effect was observed in fluctuating patients treated with rasagiline (all doses), expressed as a decrease in total Unified Parkinson's Disease Rating Scale (UPDRS) score (23.0% vs 8.5% in the placebo group). The treatment effect was still evident 6 weeks after drug discontinuation (in all doses). The safety and tolerability of rasagiline were good. Adverse events were no different than those of patients taking placebo. Almost complete platelet MAO-B inhibition was obtained at all rasagiline doses. This study has demonstrated that rasagiline (up to 2 mg/day) has a good safety profile and a beneficial clinical effect in fluctuating patients with PD when given as an add-on to chronic levodopa therapy.

PMID: 11575866 DOI: 10.1097/00002826-200011000-00005

- Safe & tolerable.
- Patients with motor fluctuations had ~23% improvement in symptoms.
- Benefit sustained 6 weeks after stopping drug.



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Y2K: Enter Rasagiline

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Rasagiline mesylate, a new MAO-B inhibitor for the treatment of Parkinson's disease: a double-blind study as adjunctive therapy to levodopa.

Rabey JM¹, Sagi J, Huberman M, Melamed E, Korczyn A, Giladi N, Inzelberg R, Djaldetti R, Klein C, Berez G; Rasagiline Study Group.

Author information

¹ Department of Neurology, Assaf Harofeh Medical Center, Zerfin, Sackler Faculty of Medicine, Tel-Aviv University, Israel.

Abstract

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- Benefit sustained 6 weeks after stopping drug.



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ADAGIO Study

N Engl J Med. 2009 Sep 24;361(13):1268-78. doi: 10.1056/NEJMoa0809335.

A double-blind, delayed-start trial of rasagiline in Parkinson's disease.

Olanow CW¹, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe W, Stocchi F, Tolosa E; ADAGIO Study Investigators.

Collaborators (129)

Author information

¹ Department of Neurology and Neuroscience, Mount Sinai School of Medicine, New York, NY 10029, USA. warren.olanow@mssm.edu

Erratum in

N Engl J Med. 2011 May 12;364(19):1882.

Abstract

BACKGROUND: A therapy that slows disease progression is the major unmet need in Parkinson's disease.

METHODS: In this double-blind trial, we examined the possibility that rasagiline has disease-modifying effects in Parkinson's disease. A total of 1176 subjects with untreated Parkinson's disease were randomly assigned to receive rasagiline (at a dose of either 1 mg or 2 mg per day) for 72 weeks (the early-start group) or placebo for 36 weeks followed by rasagiline (at a dose of either 1 mg or 2 mg per day) for 36 weeks (the delayed-start group). To determine a positive result with either dose, the early-start treatment group had to meet each of three hierarchical end points of the primary analysis based on the Unified Parkinson's Disease Rating Scale (UPDRS, a 176-point scale, with higher numbers indicating more severe disease): superiority to placebo in the rate of change in the UPDRS score between weeks 12 and 36, superiority to delayed-start treatment in the change in the score between baseline and week 72, and noninferiority to delayed-start treatment in the rate of change in the score between weeks 48 and 72.

RESULTS: Early-start treatment with rasagiline at a dose of 1 mg per day met all end points in the primary analysis: a smaller mean (+/-SE) increase (rate of worsening) in the UPDRS score between weeks 12 and 36 (0.09+/-0.02 points per week in the early-start group vs. 0.14+/-0.01 points per week in the placebo group, P=0.01), less worsening in the score between baseline and week 72 (2.82+/-0.53 points in the early-start group vs. 4.52+/-0.56 points in the delayed-start group, P=0.02), and noninferiority between the two groups with respect to the rate of change in the UPDRS score between weeks 48 and 72 (0.085+/-0.02 points per week in the early-start group vs. 0.085+/-0.02 points per week in the delayed-start group, P<0.001). All three end points were not met with rasagiline at a dose of 2 mg per day, since the change in the UPDRS score between baseline and week 72 was not significantly different in the two groups (3.47+/-0.50 points in the early-start group and 3.11+/-0.50 points in the delayed-start group, P=0.60).

CONCLUSIONS: Early treatment with rasagiline at a dose of 1 mg per day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline at a dose of 2 mg per day did not. Because the two doses were associated with different outcomes, the study results must be interpreted with caution. (ClinicalTrials.gov number, NCT00256204.)

2009 Massachusetts Medical Society

Comment in

Parkinson's disease I: glucocerebrosidase mutations, family history of melanoma and questionable effects of rasagiline. [J Neurol. 2009]

Rasagiline in Parkinson's disease. [N Engl J Med. 2010]

Rasagiline in Parkinson's disease. [N Engl J Med. 2010]

Does rasagiline have a disease-modifying effect on Parkinson's disease? [Curr Neurol Neurosci Rep. 2010]

PMID: 19776408 DOI: 10.1056/NEJMoa0809335

- 1 mg/d rasagiline associated with slower PD progression.



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Secondary Analysis

J Parkinsons Dis. 2017;7(1):117-127. doi: 10.3233/JPD-160965.

Longer Duration of MAO-B Inhibitor Exposure is Associated with Less Clinical Decline in Parkinson's Disease: An Analysis of NET-PD LS1.

Hauser RA¹, Li R², Pérez A², Ren X², Weintraub D³, Elm J⁴, Goudreau JL⁵, Morgan JC⁶, Fang JY⁷, Aminoff MJ⁸, Christine CW⁸, Dhali R⁹, Umeh CC¹⁰, Boyd JT¹¹, Stover N¹², Leehey M¹³, Zweig RM¹⁴, Nicholas AP¹⁵, Bodis-Wollner J¹⁶, Willis A¹⁷, Kiebertz K¹⁸, Tilley BC², NINDS NET-PD Investigators.

Author information

Abstract

BACKGROUND: Monoamine oxidase type B (MAO-B) inhibitors exhibit neuroprotective effects in preclinical models of PD but clinical trials have failed to convincingly demonstrate disease modifying benefits in PD patients.

OBJECTIVE: To perform a secondary analysis of NET-PD LS1 to determine if longer duration of MAO-B inhibitor exposure was associated with less clinical decline.

METHODS: The primary outcome measure was the Global Outcome (GO), comprised of 5 measures: change from baseline in the Schwab and England (ADL) scale, the 39-item Parkinson's Disease Questionnaire (PDQ-39), the UPDRS Ambulatory Capacity Scale, the Symbol Digit Modalities Test, and the most recent Modified Rankin Scale. A linear mixed model was used to explore the association between the cumulative duration of MAO-B inhibitor exposure and the GO, adjusting for necessary factors and confounders. Associations between MAO-B inhibitor exposure and each of the five GO components were then studied individually.

RESULTS: 1616 participants comprised the analytic sample. Mean observation was 4.1 (SD=1.4) years, and 784 (48.5%) participants received an MAO-B inhibitor. The regression coefficient of cumulative duration of MAO-B inhibitor exposure (in years) on the GO was -0.0064 (SE=0.002, p=0.001). Significant associations between duration of MAO-B inhibitor exposure and less progression were observed for ADL (p<0.001), Ambulatory Capacity (p<0.001), and the Rankin (p=0.002).

CONCLUSIONS: Our analysis identified a significant association between longer duration of MAO-B inhibitor exposure and less clinical decline.

These findings support the possibility that MAO-B inhibitors slow clinical disease progression and suggest that a definitive prospective trial should be considered.

KEYWORDS: MAO-B inhibitor; Parkinson's disease; disease modification; rasagiline; selegiline; treatment

PMID: 27911341 DOI: 10.3233/JPD-160965

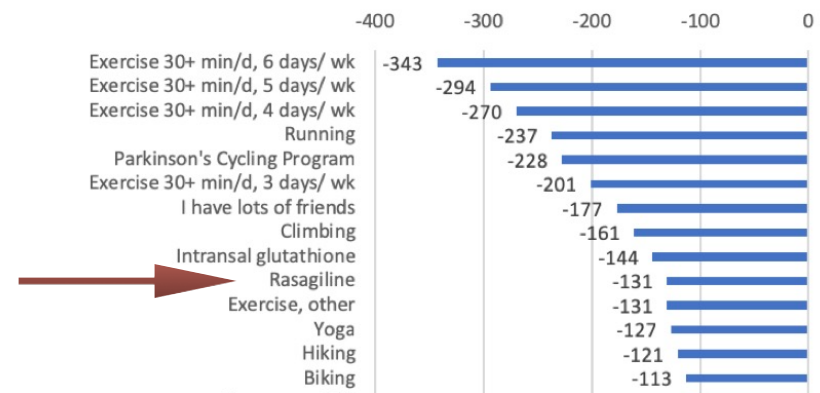
- The more years people took rasagiline, the better they did over time.



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'CAM Care PD' Data

Association with PRO-PD Score



Adjusted for age, gender, year since diagnosis, and income.

Our own [unpublished] data suggests people taking rasagiline have a slower rate of progression over time.



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Dopamine Agonists

- Ropinerole
- Pramipexole
- Rotigotine (patch)
- Apomorphine (injection)
- Bromocriptine



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Dopamine Agonist Withdrawal Syndrome (DAWS)

Drugs Aging. 2013 Aug;30(8):587-92. doi: 10.1007/s40266-013-0090-z.

Dopamine agonist withdrawal syndrome: implications for patient care.

Nirenberg MJ¹.

Author information

¹ Department of Neurology, NYU School of Medicine, New York, NY, USA. melissa.nirenberg@nyumc.org

Abstract

Dopamine agonists are effective treatments for a variety of indications, including Parkinson's disease and restless legs syndrome, but may have serious side effects, such as orthostatic hypotension, hallucinations, and impulse control disorders (including pathological gambling, compulsive eating, compulsive shopping/buying, and hypersexuality). The most effective way to alleviate these side effects is to taper or discontinue dopamine agonist therapy. A subset of patients who taper a dopamine agonist, however, develop dopamine agonist withdrawal syndrome (DAWS), which has been defined as a severe, stereotyped cluster of physical and psychological symptoms that correlate with dopamine agonist withdrawal in a dose-dependent manner, cause clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other dopaminergic medications, and cannot be accounted for by other clinical factors. The symptoms of DAWS include anxiety, panic attacks, dysphoria, depression, agitation, irritability, suicidal ideation, fatigue, orthostatic hypotension, nausea, vomiting, diaphoresis, generalized pain, and drug cravings. The severity and prognosis of DAWS is highly variable. While some patients have transient symptoms and make a full recovery, others have a protracted withdrawal syndrome lasting for months to years, and therefore may be unwilling or unable to discontinue DA therapy. Impulse control disorders appear to be a major risk factor for DAWS, and are present in virtually all affected patients. Thus, patients who are unable to discontinue dopamine agonist therapy may experience chronic impulse control disorders. At the current time, there are no known effective treatments for DAWS. For this reason, providers are urged to use dopamine agonists judiciously, warn patients about the risks of DAWS prior to the initiation of dopamine agonist therapy, and follow patients closely for withdrawal symptoms during dopamine agonist taper.

PMID: 23686524 DOI: 10.1007/s40266-013-0090-z

Withdrawal symptoms include anxiety, panic attacks, irritability, fatigue, sweating, nausea, vomiting, pain, etc.



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Managing Dyskinesia



Treating Dyskinesia With DHA Fish Oil

Ann Neurol. 2006 Feb;59(2):282-8.

Docosahexaenoic acid reduces levodopa-induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys.

Samadi P¹, Grégoire L, Rouillard C, Bédard PJ, Di Paolo T, Lévesque D.

Author information

1 Centre de recherche en Neurosciences, Centre Hospitalier Universitaire de Québec (CHUQ), Ste-Foy, Quebec, Canada.

Abstract

OBJECTIVE: The objective of the present study was to investigate the effect of docosahexaenoic acid (DHA), a polyunsaturated fatty acid (omega-3), on levodopa-induced dyskinesias (LIDs) in parkinsonian 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys.

METHODS: We explored the effect of DHA in two paradigms. First, a group of MPTP monkeys was primed with levodopa for several months before introducing DHA. A second group of MPTP monkeys (de novo) was exposed to DHA before levodopa therapy.

RESULTS: DHA administration reduced LIDs in both paradigms without alteration of the anti-parkinsonian effect of levodopa indicating that DHA can reduce the severity or delay the development of LIDs in a nonhuman primate model of Parkinson's disease.

INTERPRETATION: These results suggest that DHA can reduce the severity or delay the development of LIDs in a nonhuman primate model of Parkinson's disease. DHA may represent a new approach to improve the quality of life of Parkinson's disease patients.

PMID: 16437566 DOI: 10.1002/ana.20738

Non-human primates with levodopa-induced dyskinesia were given high dose DHA.

(Approx. 7 g DHA for a 154 lb/ 70 kg body/ d)



DHA Reduces Dyskinesia

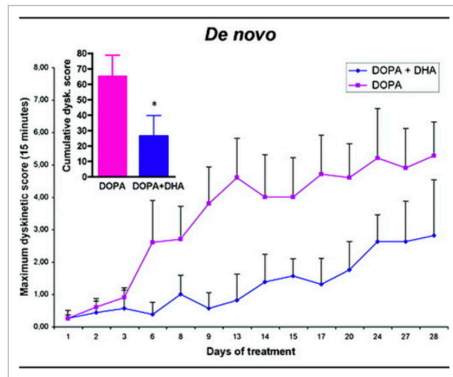


Figure 3 [Open in figure viewer](#) | [PowerPoint](#)
Time courses of the development of the maximum dyskinetic scores after L-dopa treatment in de novo 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys. Maximum dyskinetic scores obtained during the "ON" state after given treatments were daily averaged for all monkeys (N = 5 for DOPA alone and N = 4 for DOPA + DHA group). (inset) Cumulative maximal dyskinetic score for the total duration of the treatment (* $p < 0.05$ vs DOPA alone, according to a Mann-Whitney U comparison test). DHA was administered per os (gavage) at a dose of 100mg/kg for a period of 1 month.

Samadi P, et al. 2006

Almost a 50% reduction in levodopa-induced dyskinesia after 30 days DHA fish oil.

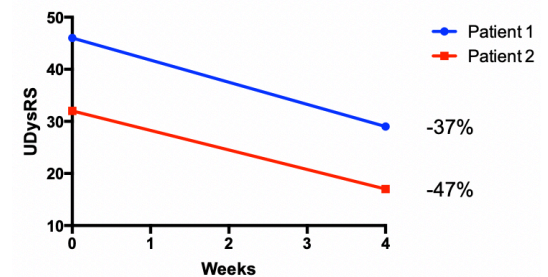


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Does it Work in Humans?



Change in Unified Dyskinesia Rating Scale following 4 weeks High DHA Fish Oil



Mischley 2013

~42% reduction in levodopa-induced dyskinesia in 2 of my patients after 1 Tbsp/d



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Make Less Levodopa Work Better



- Takes approximately 30 days for results to become fully apparent.
- Makes levodopa stronger, allowing people to reduce dose; resulting in fewer levodopa side effects (e.g. dyskinesia) without any loss of effectiveness.



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CDP-Choline (Citicoline)

Neuropsychobiology, 1982;8(6):289-96.

New strategies in the management of Parkinson's disease: a biological approach using a phospholipid precursor (CDP-choline).

Agnoli A, Ruggieri S, Denaro A, Bruno G.

Abstract

CDP-choline, an intermediate in the phospholipid metabolic pathway supposed to improve the functionality of the dopamine (DA) system, was administered to parkinsonian patients in a double-blind cross-over study versus placebo. All patients were already treated with L-dopa + dopa decarboxylase inhibitor. Clinical evaluations were carried out using the Webster Rating Scale (WRS), the Northwestern University Disability Scale (NUDS) and a semiquantitative rating scale for tremor, rigidity and bradykinesia. CDP-choline treatment showed a significant improvement of rigidity and bradykinesia and a less important amelioration of tremor. NUDS and WRS showed a similar positive result. Comparing the results obtained by placebo, we found that the actual clinical efficacy of CDP-choline regards mainly bradykinesia and rigidity (23 and 33% improvement, respectively). The positive effect of CDP-choline on parkinsonian patients already treated with L-dopa + dopa decarboxylase inhibitor stands for a possible action on the DA receptor through an activation of the phospholipid metabolism.

PMID: 7162583 DOI: 10.1159/000117914

In patients with PD on
carbidopa/levodopa, adding
CDP-choline improved slowness
& rigidity.



LK Mischley 2020

CDP-Choline (Citicoline)

Methods Find Exp Clin Pharmacol. 1985 Jan;7(1):5-8.

Oxotremorine-induced cholinergic syndrome: modifications by levodopa and/or oral cytidine diphosphocholine.

Saligaut C, Daoust M, Chadelaud M, Moore N, Chretien P, Boismare F.

Abstract

A peripheral and cerebral cholinergic syndrome was induced in mice by oxotremorine administration; pretreatment orally with cytidine diphosphocholine (CDP-choline) does not potentiate this syndrome and even antagonizes oxotremorine-induced salivation. Levodopa antagonizes the oxotremorine-induced cerebral symptoms (akinesia + tremor); however this antagonism disappears when mice are chronically pretreated orally with CDP-choline, confirming the action of CDP-choline on dopaminergic pathways. The proven efficacy of CDP-choline in Parkinsonism could then be mediated by a hypersensitivity of some cerebral dopamine receptors, and not by a direct stimulating effect of the striatal dopaminergic receptors.

PMID: 3990445

Rodent studies suggest the mechanism of action is not by directly stimulating receptors, but by making receptors more sensitive.



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CDP-Choline (Citicoline)

Clin Ther. 1988;10(6):664-71.

Clinical trial on the use of cytidine diphosphate choline in Parkinson's disease.

Cubells JM¹, Hernando C.

Author information

¹ Department of Neurosurgery, Centro Ramón y Cajal, Madrid, Spain.

Abstract

Thirty patients with Parkinson's disease, treated with levodopa for the past few years, concomitantly received 500 mg of cytidine diphosphate choline (CDPC) daily for 30 days. Significant improvements in some of the neurologic signs and in several electrophysiologic parameters measuring the traction reflex and the active contraction were observed. A greater stability of therapeutic response between doses of levodopa was also seen, although the incidence of dyskinesia increased. In a second stage of CDPC treatment, also lasting 30 days, the dose of levodopa was reduced by one-third, and the incidence of dyskinesia dropped to its previous level, but the therapeutic response remained stable. Addition of CDPC produced significant increases in plasma concentrations of dopa and homovanillic acid, with no modifications in tyrosine or 3-O-methyldopa concentrations. A significant increase in the number of lymphocytic dopaminergic receptors also occurred.

PMID: 3064905

- The addition of 500 mg/d CDP-choline enabled PwP to reduce their dose of c/l by 33%.
- The same symptomatic relief but at a lower dose.



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CDP-Choline (Citicoline)

Clin Ther. 1990 Nov-Dec;12(6):489-95.

Citicoline in the treatment of Parkinson's disease.

Eberhardt R¹, Birbamer G, Gerstenbrand F, Rainer E, Traegner H.

Author information

1 Pharmacologic Institute for Clinical Research, Munich, Germany.

Abstract

Eighty-five patients with an established diagnosis of primary Parkinson's disease were randomly assigned to receive their usual dose of levodopa (mean, 381 mg daily) plus 1,200 mg of citicoline daily or half their usual dose of levodopa (mean, 196 mg daily) plus the citicoline. Results of the Webster Rating Scale, a pegboard test, drawing, writing, and walking tests, a test of emotional state, and an overall assessment, administered before and after four weeks of treatment, revealed no significant between-group differences. Improvements on the tests were shown by more patients who received half their levodopa dose plus citicoline than by those who continued to receive their usual levodopa dose plus the citicoline. It is concluded that the levodopa-saving effect of citicoline could be used to decrease the incidence of side effects and retard the loss of efficacy of levodopa in long-term treatment.

PMID: 2289218

Adding 1200 mg/d CDP-choline and reducing levodopa dose in half was better than just adding the CDP-choline.



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CDP-Choline (Citicoline)

Clin Ther. 1991 Mar-Apr;13(2):239-42.

Citicoline in the treatment of Parkinson's disease.

Martí Massó JF¹, Urtasun M.

Author information

1 Department of Neurosciences, Universidad del País Vasco, San Sebastian, Spain.

Abstract

The subjects were 20 patients with Parkinson's disease. They were aged 52 to 76 years and the duration of the disease ranged from four to 25 years (mean, 12.5 years). All the patients were receiving levodopa alone or in combination with tricyclic antidepressants, amantadine, bromocriptine, anticholinergic agents, or lisuride. Each patient received 1,000 mg of citicoline intramuscularly daily for 15 days and then 500 mg daily for 15 days. After 30 days of treatment, the scores on the Columbia rating scale improved 7.3%; rigidity was improved 18.8%; times to walk 10 m and turn over were reduced 17.5% and 37.4%; and the handwriting test scores improved 19.7%. No side effects were reported. Four patients with advanced parkinsonian symptoms and psychotic side effects received 2,000 mg of citicoline subcutaneously or intravenously for seven days. No improvements in symptoms or treatment side effects were noted.

PMID: 1863939

- Intramuscular injections of CDP-choline led to improvements in:
 - Rigidity
 - Time to walk and turn around
 - Handwriting



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Making Levodopa Last Longer & Work Better



Dietary Protein Makes Levodopa Less Available

- Plant & animal sources of protein (eggs, soy, nuts, meat, beans, ...)
- Best to take levodopa at least 30 min before a meal.
- Take levodopa 1-3 hours after a meal, depending on the protein composition of the meal.



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Levodopa + Lemon Juice

Filters activated: Field: Title/Abstract. [Clear all](#)

Rinsho Shinkeigaku. 1994 Mar;34(3):264-6.

[Gastric acid secretion and absorption of levodopa in patients with Parkinson's disease--the effect of supplement therapy to gastric acid].

[Article in Japanese]

Yazawa I¹, Terao Y, Sai I, Hashimoto K, Sakuta M.

Author information

¹ Department of Neurology, Japanese Red Cross Medical Center.

Abstract

Since an oral regimen of levodopa has been instituted for treatment of Parkinson's disease, its absorption and metabolism has been well demonstrated. However, its chemical characteristics of high solubility in acid solution and low solubility in water have not been well known. We paid attention to this characteristic and studied the relationship between its absorption and gastric acid secretion in 38 patients with Parkinson's disease who became refractory to therapy of levodopa. We measured the pH and amount of collected fasting gastric juice. Gastric acid secretion was decreased in 22 patients (58%). In ten of these 22 patients, 30 ml of lemon juice was prescribed in every administration of levodopa as a supplement to gastric acid for two weeks. Increases of L-dopa concentration after 60 min. and 180 min. were observed after lemon juice supplement therapy. Among the Parkinson symptoms, rigidity, akinesia, and small step gait were improved in every case except one patient who showed decrease of L-dopa concentration at 180 minutes. However, improvement of tremor was less remarkable. We consider this supplement therapy to gastric acid is one of the effective and useful methods in the management of Parkinson's disease.

PMID: 8200147

- Among PwP no longer responding well to levodopa, 58% were low in stomach acid.
- Adding lemon juice to the levodopa improved rigidity, mobility, and gait.



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Levodopa + Vitamin C

Clin Neuropharmacol. 2004 Nov-Dec;27(6):270-3.

The effect of ascorbic acid on the pharmacokinetics of levodopa in elderly patients with Parkinson disease.

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Abstract

Levodopa (LD) is one of the most effective drugs for clinical symptoms in patients with Parkinson disease (PD). Most PD patients are advanced in age and may have trouble with LD absorption because aging influences drug absorption processes. Previous reports have indicated that ascorbic acid (AsA) can reduce LD dosage without losing its effectiveness. The current study sought to determine whether AsA affects LD absorption in elderly PD patients. Sixty-seven elderly PD patients took a tablet orally containing 100 mg LD and 10 mg carbidopa following an overnight fast. Plasma LD concentrations were determined at 6 points up to 3 hours, using high-performance liquid chromatography with electrochemical detection. The area under the curve (AUC), peak drug concentration (Cmax), and time to peak drug concentration (Tmax) were calculated. The pharmacokinetic evaluation was repeatedly performed 1 week later in the same way except for adding 200 mg AsA to the tablet. The changes in AUC, Cmax, and Tmax between the tests were evaluated. Significant changes in these parameters were not observed when analyzed using data from all patients. However, significant increases in AUC and Cmax, and a significant reduction in Tmax by adding AsA were observed in 25 patients with baseline AUC < or =2500 ng.hour/mL. In conclusion, AsA can improve LD absorption in elderly PD patients with poor LD bioavailability. LD therapy in combination with AsA may be one of the strategies for PD treatment.

PMID: 15613930 DOI: 10.1097/01.wnf.0000150865.21759.bc

- When vitamin C is taken with levodopa, more levodopa becomes available to the body.



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