Eltoprazine counteracts levodopa-induced dyskinesia in Parkinson's disease: A double-blind, randomised, placebo-controlled dose-finding study

Per Svenningsson,[1] Carl Rosenblad,[2] Karolina af Edholm Arvidsson,[1] Klas Wictorin,[2] Charlotte Keywood,[3] Bavani Shankar,[4] David A Lowe,[4] Anders Björklund,[5] Håkan Widner[2]

1 Department of Clinical Neuroscience and Neurology, Karolinska Institutet, 17177 Stockholm, Sweden; 2 Division of Neurology, Department of Clinical Sciences, Skåne University Hospital, 221 84 Lund, Sweden; 3 Amarantus BioScience Holdings, Inc. San Francisco, CA 94111, USA; 4 Psychogenics, Inc., Tarrytown, NY 10591, USA; 5 Neurobiology Unit, Wallenberg Neuroscience Center, Lund University, 221 84 Lund, Sweden

Aim: To examine the effect of eltoprazine against levodopa-induced-dyskinesias (LIDs) in Parkinson´s disease patients

Key results & Conclusions:

- A single oral dose of eltoprazine has beneficial antidyskinetic effects against LIDs, without altering normal motor responses to levodopa
- All doses of eltoprazine were well tolerated, with no major adverse-effects
- Eltoprazine has a favourable benefit-risk profile and pharmacokinetics in PD-LID patients
- The data support further longer term clinical studies with eltoprazine to treat LIDs

Background

In advanced Parkinson´s disease, serotonergic terminals take up levodopa and convert it to dopamine. Abnormally released dopamine may contribute to the development of levodopa-induced-dyskinesia (LID). Simultaneous activation of 5-HT_{1A} and 5-HT_{1B} receptors blocks LID in animal models of dopamine depletion, justifying a clinical study with the $5HT_{1A/1B}$ partial agonist eltoprazine, in PD-LID patients.

Objectives and Methods

A double-blind, randomized, placebo-controlled, dose-finding phase I/IIa study was conducted. Following a placebo test session, patients with LID (n = 22) were randomised to single oral doses of placebo and eltoprazine, at 2.5, 5, and 7.5 mg in 4 sequence groups. These were administered with a challenge dose of levodopa (150% of usual dose) and the patients observed for 3 hours post dose.

Primary efficacy variables: Clinical Dyskinesia Rating Scale (CDRS) AUC_{0-3} and maximum change in UPDRS Part III during three hours post dose.

Secondary measures included maximum CDRS score, Rush Dyskinesia Rating Scale (RDRS) score AUC_{0-3}, Hospital Anxiety Depression Scale and Montgomery Asberg Depression Rating Scale, eltoprazine pharmacokinetics and adverse events

A Wilcoxon Signed Ranked Test was used to compare each eltoprazine dose level to paired randomized placebo on the primary efficacy variables; mixed model repeated measures (MMRM) was used for *post hoc* analyses of the AUC_{0-3} and peak dose CDRS

Patient demographics

- Age years (SD) 66.6 (8.8)
- Male 16/female 6 , Caucasian 22
- PD duration: years (SD) 11.6 (3.1)
- LID duration years (SD) 3.41 (1.40)
- Hoehn and Yahr stage (SD) 2.86 (0.44)
- Peak-dose dyskinesias 22 (100%)
- L-DOPA 22 (100%) LED (mg) 1191 (495)
- DA 17 (77%),MAOB inh 9 (41%), COMT inh 15 (68%)

Efficacy

For 3 hours following levodopa challenge, eltoprazine 5 mg significantly reduced CDRS AUC_{0-3} (-1.02(1.49); p=0.004)); RDRS AUC_{0-3} (-0.15(0.23);p=0.003)); and maximum CDRS(-1.14(1.59);p=0.005)).

Post hoc analysis confirmed these results and also showed eltoprazine 5 mg (p = 0.035) and 7.5 mg (p = 0.043) significantly reduced peak dose dyskinesia.

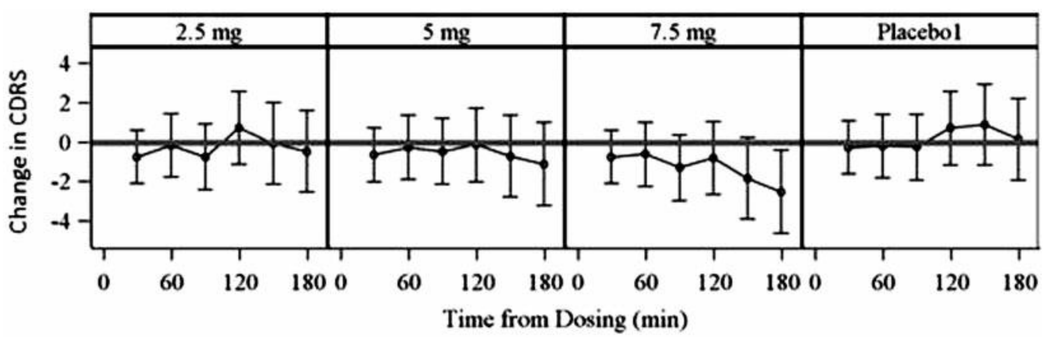
PD motor function was unaffected; UPDRS Part III scores did not differ between placebo and eltoprazine.

There were no adverse effects of eltoprazine on mood.

Table of primary efficacy

Variable	Test Session 1 Placebo	Rando Placebo	Elto 2.5 mg	Elto 5 mg	Elto 7.5 mg	Rando Placebo – Test Placebo	Elto 2.5 mg – Rando Placebo	Elto 5 mg – Rando Placebo	Elto7.5 mg – Rando Placebo
CDRS AUC_{0-3}	7.53 (2.90)	7.48 (2.71)	6.84 (2.63)	6.47 (2.20)	7.06 (2.35)	-0.04 (1.66) p=0.975	-0.64 (1.63) p=0.065	-0.102 (1.49) p=0.004 **	-0.043 (1.33) p=0.103
Change in UPDRS Part III	2.41 (4.85)	3.46 (5.76)	0.93 (8.08)	2.29 (6.04)	3.95 (5.84)	1.05 (4.04) p=0.272	-2.52 (9.11) p=0.053	-1.17 (6.62) p=0.156	0.49 (8.60) p=0.375

Post hoc analyses of CDRS scores



Safety and pharmacokinetics

All doses of eltoprazine were well tolerated. Most common adverse effects (>10%) were nausea, dizziness, fatigue and arthralgia.

Eltoprazine plasma concentrations (n = 12) increased dose proportionally with a mean T_{max} of 2.5 hours

Reference

Svenningsson P, Rosenblad C, Af Edholm Arvidsson K, Wictorin K, Keywood C,Shankar B, Lowe DA, Björklund A, Widner H. Eltoprazine counteracts l-DOPA-induced dyskinesias in Parkinson's disease: a dose-finding study. Brain. 2015 138:963-73.