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

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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 antidysskinetic 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-HT1A and 5-HT1D receptors blocks LID in animal models of dopamine depletion, justifying a clinical study with the 5HT1A/1D 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) AUC0-3 and maximum change in UPDRS Part III during three hours post dose.
Secondary measures included maximum CDRS score, Rush Dyskinesia Rating Scale (RDRS) score AUC0-3, 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 AUC0-3 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%)

Table of primary efficacy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test Session 1 Placebo</th>
<th>Placebo</th>
<th>Elto 2.5 mg</th>
<th>Elto 5 mg</th>
<th>Elto 7.5 mg</th>
<th>Rando Placebo</th>
<th>Elto 2.5 mg – Rando Placebo</th>
<th>Elto 5 mg – Rando Placebo</th>
<th>Elto7.5 mg – Rando Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDRS AUC0-3</td>
<td>7.53 (2.90)</td>
<td>7.48 (2.71)</td>
<td>6.84 (2.63)</td>
<td>6.47 (2.20)</td>
<td>7.06 (2.35)</td>
<td>-0.04 (1.66)</td>
<td>0.975</td>
<td>-0.64 (1.63)</td>
<td>0.065</td>
</tr>
<tr>
<td>Change in UPDRS Part III</td>
<td>2.41 (4.85)</td>
<td>3.46 (5.76)</td>
<td>0.93 (8.08)</td>
<td>2.29 (6.04)</td>
<td>3.95 (5.84)</td>
<td>1.05 (4.04)</td>
<td>0.272</td>
<td>-2.52 (9.11)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

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 1max of 2.5 hours

Reference