High dose naltrexone for dyskinesias induced by levodopa

A J Manson, R Katzenschlager, J Hobart, A J Lees

Abstract
Ten patients with Parkinson’s disease and levodopa induced dyskinesias (LIDs) took part in this randomised, placebo controlled, double blind, crossover trial to assess the efficacy and tolerability of high dose oral naltrexone for LIDs in Parkinson’s disease. Patients received naltrexone (5 mg/kg/day) or placebo for 2.5 weeks with 1 week wash out in between. Dyskinesias and motor function were assessed with a levodopa challenge, unified Parkinson’s disease rating scale (UPDRS), the unified dyskinesia rating scale (UDRS), and patient diaries. Eight patients completed the trial. There was a small reduction in LIDs measured by patient diaries with naltrexone (20.5 (SD 24.9)% compared with placebo (−4.1 (SD 22.6)%), p<0.05, although no difference was found by other subjective or objective measures. Naltrexone was well tolerated and caused no significant differences in UPDRS motor scores or off time. This study suggests that short term therapy with high dose naltrexone (250–350 mg/day) has no or minimal effect on reducing LIDs in Parkinson’s disease.

Keywords: naltrexone; levodopa induced dyskinesias; Parkinson’s disease

Levodopa induced dyskinesias (LIDs) are a considerable challenge in the long term management of Parkinson’s disease. Recently, non-dopaminergic pathways have been targeted as a means of controlling dyskinesias without worsening parkinsonism, and promising results with the glutamate antagonist amantadine have been reported. However, recent studies with the MPTP lesioned marmoset model of Parkinson’s disease demonstrated a marked reduction of LIDs with oral naltrexone at doses of 10 mg/kg/day. The aim of this study was to investigate the antidyskinetic effect of higher dose naltrexone (5 mg/kg/day).

Methods
Ten patients (six men and four women) with idiopathic Parkinson’s disease participated in the trial. Their mean age was 62 (range 53–80) years, mean duration of Parkinson’s disease, 13.2 (range 8–22) years, and mean duration of levodopa therapy, 11.5 (range 7–17) years. Six patients were taking oral dopamine agonists (mean pergolide equivalent dose 3.2 mg/day), one was on a continuous amorphine infusion, and two were taking amantadine. All had disabling LIDs and had been receiving a fixed dose of their usual antiparkinsonian medication for a period of at least 1 month before inclusion. Exclusion criteria included patients with moderate to severe hepatic impairment, concurrent use of opioid containing medication or opiate dependency, hypersensitivity to naltrexone, and moderate to severe dementia. All patients gave informed consent to participate and the joint medical ethics committee of the National Hospital for Neurology and Neurosurgery approved the study.

Baseline screening tests, performed between 1 and 2 weeks before the start of the study, included a full medical history and examination, mini mental state examination, an ECG, full blood count, urea, electrolytes, and liver function testing. The trial was double blind, placebo controlled, and crossover in design with 2.5 weeks on each treatment separated by 1 week for washout. Patients were given oral naltrexone (5 mg/kg (to the nearest 50 mg)), in three divided doses, to be taken after meals. The dose was gradually increased from 100 mg to 50 –100 mg increments a day over the 3 to 4 days of each treatment period.

Patients were assessed with levodopa challenges, at baseline, and at the end of each treatment period. The challenges were performed in a standard fashion using the patient’s normal maximum dose (range 100–300 mg) required to achieve the on state and assessed after an overnight fast and withdrawal of medication (except naltrexone), using Hoehn and Yahr...
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Results are means (data ranges or SD as appropriate)

fied dyskinesia rating scale (UDRS) before cards for five days and the Lang and Fahn uni-
ing a maximum score of 24. Both scales were
Orofacial and buccolingual, global, and dental
scale (UPDRS) in the o

3–5 (excluding phenomenological rating) and
the modified AIM scale, for task 1 and 2.11 13

Interrater reliability for the blinded objective
dyskinesia rating was good for both scales. Pearson’s r between the two raters’ scores for
AIMS was 0.86 (p<0.01), with a mean difference between scores of 0.6 (SD 0.3).
Spearman’s r for the Goetz scale was 0.67 (p<0.01), with a mean difference between
raters’ scores of 0.3 (SD 0.2).

No change in daily on times or objective
UPDRS scores were found between the two
treatment periods.

Severe nausea and vomiting led to with-
drawal on the first day of naltrexone treatment
in one patient. The patient had inadvertently
taken 350 mg naltrexone, without titrating up
the dose, on an empty stomach. Two further
patients reported moderate to severe anorexia
during the naltrexone treatment period but
were able to continue. Naltrexone was other-
wise well tolerated and there were no changes
in liver function. There were no adverse events
during the placebo phase.

Discussion

A very mild subjective improvement in dyski-
nesia occurred with naltrexone (5 mg/kg/day).
No improvement was seen with objective
measures, and only two patients reported a
moderate improvement of dyskinesias with
naltrexone, which was not different from
placebo. Although the patient numbers were
small, this study was designed to investigate a
clinically relevant antidyskinetic effect, which
has been shown to be possible by careful and
detailed analysis of small samples.3 15

Table 1 Effect of high dose naltrexone and placebo on dyskinesia by all measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Mean (range/SD)</th>
<th>Placebo Mean (range/SD)</th>
<th>Naltrexone Mean (range/SD)</th>
<th>P-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective dyskinesia ratings:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean AIM scores (max 24)</td>
<td>9.3 (4.8–12.7)</td>
<td>10.2 (7.25–13.1)</td>
<td>9.8 (7–14.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Mean % reduction AIMS scores</td>
<td>−13.4 (20.1)</td>
<td>−9.4 (22.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Goetz scores (max 4)</td>
<td>1.5 (0.8–2.4)</td>
<td>1.5 (1.0–2.1)</td>
<td>1.5 (1.0–2.0)</td>
<td></td>
</tr>
<tr>
<td>Mean % reduction Goetz scores</td>
<td>0.003 (0.002)</td>
<td>0.007 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective impression:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diary scores</td>
<td>5.5 (3.9–7.7)</td>
<td>5.51 (3.5–8.3)</td>
<td>4.4 (2.7–8.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean % reduction diary scores</td>
<td>−4.1 (22.5)</td>
<td>20.5 (24.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean UDRS score</td>
<td>12.1 (10–16)</td>
<td>1.7 (1.0)</td>
<td>0.3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Mean % reduction UDRS scores</td>
<td>9.7 (18.7)</td>
<td>11.2 (16.3)</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Mean % reduction UPDRS item 3 (dyskinesia severity)</td>
<td>9.4 (18.4)</td>
<td>12.5 (35.4)</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Mean % reduction UPDRS item 3 (dyskinesia duration)</td>
<td>18.7 (57.2)</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are means (data ranges or SD as appropriate)

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Naltrexone may exert a very small antidyskinetic effect, which could only be detected by patient diaries. As these do not have a standardised scale, but work via VASs, based on individual patients' severity ranges, they are potentially more sensitive. However, it seems improbable that an important clinically relevant antidyskinetic effect has been missed.

Several non-dopaminergic drugs, including opioid antagonists, have been reported to have potent antidyskinetic effects in animal models, and this study illustrates the difficulty in translating these results to clinical practice. A possible explanation for this discrepancy could be the relatively lower dose of naltrexone (5 mg/kg/day) used in our study, compared with 10 mg/kg/day used in the MPTP lesioned marmosets. However, the dosage used was the maximum allowed by our centre's ethics committee, due to concerns about increases in serum transaminases. Doses up to 800 mg/day have, however, been shown to be well tolerated and non-toxic in volunteers and clinical trials in psychiatric disorders, and long term treatment for opiate addiction with 350 mg/day has proved safe.

Naltrexone is active at µ, δ, and κ receptors, and antagonism at κ and δ opioid receptors could potentially reduce LIDs through modulation of the direct and indirect striatopallidal pathways, as previously described. However, naltrexone is preferentially active at µ receptors, and although these have been implicated in LID generation, the selective µ antagonist cyprodime failed to suppress involuntary movements in the rat model of LID. It is therefore possible that naltrexone's activity at δ receptors at the dosage used is inadequate to attenuate dyskinesia.

Although the previous clinical and preclinical studies successfully demonstrating an antidyskinetic effect did so acutely, it is conceivable that resetting of the receptors may require longer treatment periods. Reduction of dyskinesia with apomorphine monotherapy usually takes 3 to 6 months.

Studies with higher doses of naltrexone or for longer treatment periods may therefore be warranted.

We thank Dupont Pharma for the supply of Naltrexone, Mike O'Sullivan for helping with the video challenges, and The Berta Lila Weston Institute for funding.

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