Randomized clinical trial of topiramate for levodopa-induced dyskinesia in Parkinson's disease

Christopher Kobylecki[1,2]*
David J Burn[3]
Lewis Kass-Iliyya[1,2]
Mark W Kellett[2]
Alan R Crossman[4]
Monty A Silverdale[1,2]

1. Centre for Clinical and Cognitive Neurosciences, Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, U.K.
2. Department of Neurology, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, U.K.
3. Institute for Ageing and Health, Newcastle University, Newcastle, U.K.
4. Faculty of Life Sciences, University of Manchester, Manchester, U.K.

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*corresponding author
Dr Christopher Kobylecki
Department of Neurology
Greater Manchester Neurosciences Centre
Salford Royal NHS Foundation Trust
Salford M6 8HD
U.K.
Tel: 0044 161 2064279
Fax: 0044 161 2062993
Email: christopher.kobylecki@manchester.ac.uk

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Abstract

Background

The antiepileptic drug topiramate reduces levodopa-induced dyskinesia without exacerbating parkinsonism in animal models. We report a randomized, double-blind, placebo-controlled crossover trial in patients with Parkinson's disease and levodopa-induced dyskinesia.

Methods

Fifteen patients with Parkinson's disease and stable levodopa-induced dyskinesia were enrolled into the study, of whom 13 were randomized to topiramate or placebo. The study medication was titrated to 100 mg/day over four weeks, and assessments were carried out after a further two weeks. Dyskinesia severity assessed by a blinded rater from video recordings was the primary outcome measure.

Results

Seven patients (mean age 58.9 ± 12.8 years) completed the study. Patients taking topiramate *vs* placebo showed a significant increase in dyskinesia severity compared to baseline (Wilcoxon signed rank test, P=0.043). Five patients withdrew from the study whilst taking topiramate due to adverse effects.

Conclusions

Topiramate tended to worsen dyskinesia in patients with Parkinson's disease, and was poorly tolerated.

Levodopa-induced dyskinesia (LID) complicates dopaminergic therapy of Parkinson's disease (PD) in the majority of patients, and impacts adversely upon their quality of life. Proven pharmacological treatment options for dyskinesia are relatively few. Amantadine, an antagonist at glutamatergic N-methyl-D-aspartate receptors, is the mainstay of anti-dyskinetic therapy, but is not tolerated in a significant number of patients [1].

The mechanisms of LID are complex, but include overactivity of corticostriatal glutamatergic transmission. Changes in striatal α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor expression have been reported in dyskinetic PD patients [2]. AMPA receptor antagonists have antidyskinetic effects in animal models of LID [3, 4]. We have previously shown that the antiepileptic drug topiramate, a negative modulator of AMPA receptors, alleviates LID in both the 6-hydroxydopamine (6-OHDA)-lesioned rat and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned nonhuman primate models of PD and LID [5, 6]. The potential anti-dyskinetic properties of topiramate have not as yet been examined in the clinical setting. We report a double-blind, placebo-controlled crossover trial of topiramate for LID in patients with PD. We hypothesized, based on the preclinical data, that topiramate would reduce dyskinesia in patients with LID, without significantly worsening parkinsonism.

Methods

A total of 15 patients with idiopathic PD (mean age 58.9±9.9 years, range 42-75), with stable L-DOPA-induced dyskinesia and on a stable dose of antiparkinsonian medications, were assessed for inclusion into the study. Recruitment was from specialist movement disorder clinics at Greater Manchester Neurosciences Centre, Salford, and Newcastle upon Tyne Hospitals NHS Trust. Exclusion criteria included hypersensivity to topiramate or its excipients, prior surgery for PD, dementia as defined by a MMSE score≤24, liver or renal disease and past history of nephrolithiasis. Concomitant use of other anti-epileptic drugs, carbonic anhydrase inhibitors, metformin or digoxin was also prohibited. The study flow

chart is summarized in figure 1. All patients gave written informed consent to participate in the study, which was approved by Leeds (West) Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency (EudraCT number:2007-002467-27). The study was ISRCTN registered (number: 95151471) prior to the enrollment of the first participant.

Eligible patients (ten of whom were treated with amantadine) were randomized to receive identical capsules of topiramate 25 mg or placebo in a double-blind crossover design. The dose was escalated by one capsule/week over four weeks up to a target dose of 100 mg (4 capsules) per day in two divided doses, followed by a maintenance phase of two weeks. Clinical and video assessments were carried out at baseline (pre-randomisation) and at the end of each study arm. The dose of study medication was tapered down over two weeks at the end of each study arm, with a two-week washout period between study arms. At each of the three study visits, patients attended having not taken their antiparkinsonian medication for 12 hours. Video recordings and UPDRS-III scoring were undertaken in the 'off' state and every 30 minutes for 150 minutes following administration of the patient's normal antiparkinsonian medications and study medication.

The primary outcome measure was dyskinesia severity area under the curve (AUC) as measured using a five-point severity rating in seven body parts [7]. Dyskinesia was scored as follows: 0=no dyskinesia; 1=questionable or mild dyskinesia; 2=moderate amplitude but quite apparent abnormal postures or movements that are not intrusive; 3=large amplitude movements or postures that may distort and mildly or moderately disturb voluntary movements; 4=severe and grotesque postures of movements that markedly disturb posture or ongoing voluntary activities [7]. Dyskinesia AUC was calculated using the trapezium method. In order to detect a 20% reduction in dyskinesia AUC compared to baseline, recruitment of 19 patients was estimated to yield 80% power.

Video recordings were assessed by a trained rater blinded to treatment allocation who had not been involved in the clinical study. Secondary outcome measures include investigator-rated parkinsonian disability as measured by UPDRS-III, and subject-rated impairment measured by the Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS) [8], patient global impression of change (PGI), and UPDRS-IV. In order to detect negative effects on mood, the Geriatric Depression Scale (GDS-15) was recorded at baseline, during drug titration and at the end of each treatment arm.

Data were tested for normality of distribution and were compared using appropriate statistical tests using SPSS 20 (IBM Software). The primary outcome measure was compared between topiramate and placebo groups using non-parametric Wilcoxon signed rank test. Categorical data were compared using Fisher's exact test. A significance level of $P<0.05$ was used for all analyses.

Results

A total of seven patients (4 male, 3 female) completed both arms of the study and were included in the final analysis; their demographic information is given in table 1. Five of seven patients were taking amantadine on enrollment to the study. The difference in dyskinesia severity from baseline as measured by AUC was greater in patients receiving topiramate compared to placebo ($P=0.043$). There was no significant difference in 'off' UPDRS-III scores between groups, and no difference between baseline dyskinesia scores of those treated initially with topiramate compared to placebo ($P>0.05$). Patient-related dyskinesia severity as rated by PGI-I or UPDRS-IV did not show significant differences between topiramate and placebo. No differences were identified in dyskinesia-related impairment of ADLs as measured by the LFADLDS, or depression scores as measured by the GDS-15 (Table 1).

Adverse events were seen in four patients receiving placebo (median 0.5 per patient, range 0-3 AEs) and nine who received topiramate (median 3 per patient, range 0-10 AEs). The most common AEs in patients receiving topiramate were

dry eyes/mouth (5 cases), cognitive adverse effects including hallucinations (6), worsening dyskinesia (3), anxiety/depression (3) and breathing problems (3). Five patients in total withdrew from the study due to adverse events on topiramate, while only one withdrew whilst taking placebo (Figure 1). There was no difference in the proportion of patients treated with amantadine who withdrew from the study compared to those who completed the study (P>0.05). One serious adverse event was noted in a patient taking topiramate.

Discussion

We report the first published randomized double-blind placebo-controlled trial of topiramate for levodopa-induced dyskinesia. Contrary to preclinical studies, patients receiving topiramate experienced a significant worsening of dyskinesia severity from baseline compared to those treated with placebo. There was no evidence for worsening of parkinsonism in patients on topiramate, but it appeared to be poorly tolerated compared to placebo.

Our study did not achieve its projected recruitment targets, due in part to the high drop-out rate of patients in the topiramate arm. While the study is therefore underpowered to detect the hypothesized changes, the relative increases in dyskinesia seen in the topiramate arm were robust and present in the majority of patients, and therefore seem unlikely to have been a type I error. However, larger studies would be required to confirm this observation. The possibility that the finding relates to a bias from those dropping out of the study is unlikely, as patients with worsening dyskinesia would presumably have been more likely to withdraw from the study.

Topiramate has previously been shown to reduce severity of abnormal involuntary movements in the 6-OHDA-lesioned rat model of LID, as well as the MPTP-lesioned marmoset [5, 6]. The worsening of dyskinesia seen in the current study can be understood by several potential mechanisms. The dyskinesia scale used in the marmoset assessments assesses dyskinesia-related disability whilst that used in the clinical trial focuses on dyskinesia intensity; such discrepancies

may limit the success of translating preclinical studies of antidyskinetic agents [9]. In addition, patients in the study received up-titration of topiramate over four weeks followed by two weeks maintenance, compared to acute administration of single doses of topiramate in both the rodent and nonhuman primate studies. It is possible that tolerance to the initial effects of topiramate occurs with chronic treatment, which was not modeled in the preclinical studies. This highlights the importance of standardizing as much as practicable the drug administration schedule between preclinical and clinical studies [9]. The possibility that the dose of topiramate used in this study was too low to exert a biological effect is unlikely, as it is well within the dose range found to be relevant to pharmacodynamic effects in epilepsy and migraine [10]. It seems unlikely that higher doses would be well tolerated based on the safety data presented here.

With regard to the mechanism of action of topiramate, it has been shown to modulate AMPA receptor function by reducing phosphorylation of GluR1 subunits [11]. Again, it is unclear whether chronic treatment has the same effects. Previous work from our group suggests that blockade of GluR1-containing Ca^{2+}-permeable AMPA receptors may be an important mechanism of antidyskinetic action [4]. Topiramate was found to reduce AMPA-induced Ca^{2+} transients in cell cultures, although the dose-response curve was U-shaped [11], implying that higher doses might not be associated with this effect, and could lead to paradoxical worsening of dyskinesia. Studies of the AMPA receptor antagonist perampanel in PD patients have failed to show beneficial effects on LID, although on-time rather than dyskinesia was the primary outcome measure in all of the studies thus far reported [12].

The fact that the majority of our patients were taking amantadine together with topiramate is a limitation of the study, although preclinical data suggest a synergistic antidyskinetic effect [6]. It is possible that co-treatment with amantadine could impair tolerability of topiramate, although the proportion of patients co-treated with amantadine was no different between those withdrawing from the study compared to those completing treatment. Generally

our findings suggest that topiramate is not well tolerated in the PD population, with a relatively high incidence of adverse events prompting withdrawal from the study. Most of these, including neurocognitive adverse events, were predictable from the known clinical profile of topiramate [10]. It is also possible that topiramate could have a pharmacokinetic interaction with amantadine leading to reduced antidyskinetic efficacy, although we are unaware of any published data regarding this [10].

Our findings, although subject to the limitations discussed above, suggest that topiramate may not be a useful future anti-dyskinesia approach for PD. Larger studies may be required to confirm our initial observations. Future work should also focus on the investigation of subtype-selective AMPA receptor antagonists and their effects during chronic treatment in animal models of LID, in order better to understand the utility of AMPA receptor modulation in this condition.

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Author roles

Kobylecki: Research project: conception, design, organization, execution; Statistical analysis: design, execution; Manuscript: writing of first draft and subsequent revisions.

Burn: Research project: organization, design, execution; Statistical analysis: review and critique; Manuscript: review and critique.

Kass-Iliyya: Research project: video analysis; Manuscript: review and critique.

Kellett: Research project: organization; Manuscript: review and critique.

Crossman: Research project: conception, design; Manuscript: review and critique.
Silverdale: Research project: conception, design, organization, execution, supervision; Statistical analysis: design; Manuscript: review and critique.

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Figure and table legends

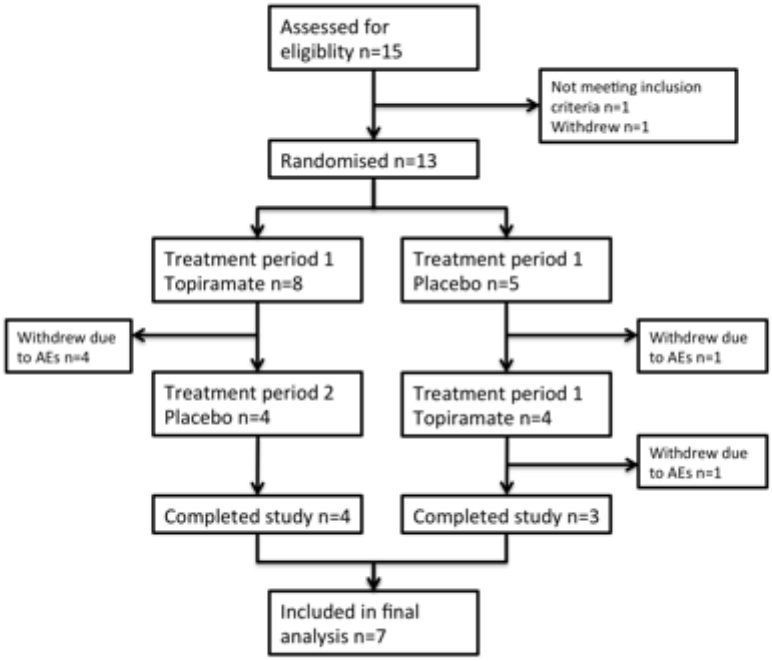

Figure 1

Flow diagram of patients enrolled into the trial.

Table 1

Demographic information of patients completing trial, and details of outcome measures at baseline and at the end of topiramate and placebo study arms. Data are presented as mean ± S.D. unless otherwise stated. AUC, area under the curve; UPDRS, Unified Parkinson's Disease Rating Scale; PGI-I, patient global impression of improvement; LFADLDS, Lang-Fahn Activities of Daily Living Dyskinesia Scale; GDS, Geriatric Depression Scale. * $P<0.05$ compared to placebo group (Wilcoxon signed rank test).

Demographic information			
Age (years)		58.9 ± 12.8 (42-75)	
PD duration (years)		12.4 ± 5.4 (5.8-21.5)	
Dyskinesia duration (years)		4.5 ± 3.7 (1.5-10.5)	
Hoehn and Yahr 'off' score (median, range)		2.0 (2.0-4.0)	
Levodopa equivalent dose (mg)		1344 ± 404 (825-2125)	
Study outcome measures			
	Baseline	Placebo	Topiramate
Dyskinesia AUC	1122 ± 496	1249 ± 536	1847 ± 744
Difference in AUC from baseline	-	126 ± 251	724 ± 411*
UPDRS-IV sum 32+33 (median, range)	4.0 (1.0-7.0)	4.0 (1.0-5.0)	2.0 (2.0-5.0)
Difference in UPDRS-IV sum 32+33	-	0.0 (-2.0-1.0)	-2.0 (-3.0-1.0)
UPDRS-III 'off'	31.4 ± 12.3	29.6 ± 10.0	30.6 ± 9.4
PGI-I score (median, range)	-	4.0 (3.0-5.0)	3.0 (2.0-7.0)
LFADLDS score	10.3 ± 5.3	10.3 ± 3.9	11.0 ± 3.7
GDS-15 score	7.7 ± 2.2	6.6 ± 1.8	6.0 ± 1.2