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Cannabinoid, CB1 agonists in cervical dystonia: Failure in a phase IIa randomized controlled trial

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ABSTRACT

Background: Dystonia may result from reduced GABAergic transmission in the external globus pallidus (GPe). Cannabinoid CB1 agonists enhance GABA in the GPe and may therefore reduce dystonia.
Objectives: To determine the efficacy of the cannabinoid CB1 agonist, dronabinol, in cervical dystonia (CD).
Methods: Nine patients with CD were randomised to dronabinol (15 mg/d)/placebo in an 8-week cross-over trial. Outcome measures included TWSTRS, visual analog scale of pain, global impression of change and adverse events (AEs).
Results: There was no effect of dronabinol compared to placebo on any outcome measure (all $P > 0.05$, $n = 7$). One subject withdrew due to AEs and one was lost to follow-up. Mild AEs were experienced by all.
Conclusions: Short–term use of dronabinol in CD has no benefit. Despite the study limitations, cannabinoids are unlikely to be useful in the treatment of dystonia.

Introduction

Idiopathic cervical dystonia (CD) is the most common form of focal dystonia [1]. To date, oral pharmacological treatments have had limited efficacy and often poor tolerability in CD. The most effective therapy in current use is botulinum toxin, however, repeated injections are required every 3–4 months from an experienced clinician and there are subgroups of patients who do not respond or who may become secondary non responders due to the development of blocking antibodies to the toxin [2]. Thus, alternative therapeutic options are required.

The neural mechanisms underlying dystonia are not well understood but in keeping with findings in other hyperkinetic movement disorders, may involve underactivity of the output regions of the basal ganglia; the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNR) [3]. In support of this, electrophysiological recordings from patients with idiopathic dystonia undergoing surgery have demonstrated very low firing rates in GPi neurons [4]. A key abnormality responsible for underactivity of the GPi may be increased inhibitory GABAergic transmission from the external globus pallidus (GPe) [5–7]. Thus reducing GABAergic transmission in the GPe may reduce dystonia. One method of reducing GABAergic transmission may be via stimulation of cannabinoid receptors.

High levels of cannabinoid, CB1 receptors are found in the globus pallidus and SNR [8] and are located presynaptically on the GABA terminals of striatal projection neurons [9,10]. Recent positron emission tomography studies have confirmed these findings in human subjects [11]. Cannabinoids function as neuromodulators and enhance GABA transmission in the GPe [12], possibly by reducing GABA reuptake [13], although the exact mechanism remains unclear [14,15]. Furthermore, infusion of cannabinoids into the rodent globus pallidus results in a decrease in activity of pallidal neurons [16,17]. Thus, cannabinoid receptor stimulation may reduce overactivity of the GPe and thereby reduce dystonic symptoms.

In support of this, the synthetic cannabinoid agonist, WIN 55–212, has been shown to enhance the antidystonic effects of benzodiazepines in a genetic rodent model of generalized dystonia [18]. There are currently no validated primate models of idiopathic dystonia but levodopa-induced dystonia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned primate model of PD may model the neural mechanisms that underlie symptoms of idiopathic dystonia in man. In the MPTP-lesioned primate, levodopa induced dyskinesia, characterized by both dystonia and chorea, are reduced by systemic administration of the synthetic cannabinoid receptor agonist nabilone [19].

We have previously assessed the tolerability and efficacy of a single dose of the synthetic cannabinoid, nabilone in subjects with

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focal and generalized dystonia in a double blind randomised controlled study; this demonstrated tolerability but no significant effect on dystonia [20]. In a similar acute dose setting, nabilone was assessed in Parkinson's disease patients, both off and on levodopa, with a significant improvement in levodopa-induced dyskinesia but of interest there was also an improvement in painful limb dystonia occurring prior to treatment with levodopa – so called 'off-period' dystonia in 2 subjects [21]. Therefore, we proposed to assess the benefit of another synthetic cannabinoid agonist, dronabinol, on dystonia over a 3 week treatment period. Dronabinol has been widely used in the treatment of anorexia and nausea in chemotherapy patients and has shown good safety and tolerability in that population [22,23]. Due to the heterogeneity and variability in clinical severity of dystonia, we assessed dronabinol only in patients with idiopathic cervical dystonia (CD) using a double-blind, randomized, placebo controlled crossover design.

Methods

Male and female subjects, aged 18–75 yrs, with CD were recruited from the Toronto Western Hospital movement disorders center between January 2007 and May 2009. Exclusion criteria included secondary causes of dystonia, active or prior psychosis, history of substance abuse, use of any other cannabinoids in the preceding month, refusal to refrain from operating heavy machinery or driving during the trial. Subjects had to be at least 4 months since the time of their last botulinum toxin injection. The use of other GABA mediated drugs including gabapentin, phenobarbital, benzodiazepines, or baclofen were only allowed if patients were on a stable dose for at least a month prior to the initiation of the study. Any other medications that might affect dystonia remained unchanged during the trial and no new treatments were initiated during the trial. Subjects were required not to use marijuana or any other cannabinoid aside from the study drug during the trial period. Patients were randomized in a cross-over design, to placebo followed by dronabinol or vice versa by the use of computer-generated random numbers table that remained within the hospital pharmacy until the end of the trial.

Dronabinol tablets (Marinol®, purchased from Solvay Pharma, Markham, ON), consisted of 2.5 mg delta 9 tetrahydrocannabinol(Δ^9-THC), and matching placebo tablets were produced by the hospital pharmacy. Dronabinol/placebo was commenced at 1 tablet (2.5 mg) OD and increased every 3 days up to 3 tabs BID (maximum dose 15 mg)/d over 12 days and then maintained for 9 days. Subjects were contacted by phone every third day to assess side effects in order to determine dose escalation. If the subject could not tolerate a dose escalation, then the dose was reduced to the preceding level and continued down until tolerated. Subjects were required to maintain a stable dose for a minimum of 4 days prior to each assessment. At the end of the third week, study drug was reduced to stop over 3 days followed by a 2 week washed out period and an identical titration and maintenance treatment for the second arm. Given the 25–36 h half-life of dronabinol a 2 week wash-out was adequate. Compliance was monitored by phone calls for side effects and pill counts were performed at the end of each treatment arm. The total study duration was 8 weeks. The study was conducted in accordance with Good Clinical Practice and was approved by the University of Toronto research ethics board. The study was registered at clinical trials.gov (NCT00418925). All patients gave written informed consent.

The primary outcome measure was the change in the Toronto Western Hospital Spasmodic Torticollis Rating Scale (TWSTRS) part A subscore, at the beginning and end of each 3 week treatment phase, between dronabinol and placebo. TWSTRS is a validated rating scale used in the assessment of CD [24,25] consisting of three parts. TWSTRS Part A measures CD motor severity (score 0–35, a higher score indicates greater severity) and was determined from a standardized video protocol, outlined in the TWSTRS scale, performed at each visit, and then scored *post hoc* by a blinded investigator who was not involved in the study visits. TWSTRS part B is a subjective rating of CD disability related to activities of daily living (score 0–33) and part C measures pain related to CD (score 0–20). A second investigator assessed secondary outcomes at each study visit including TWSTRS parts B and C, global impression scale (GIS), a visual analog pain (VAP) scale and adverse events.

Sample size

To our knowledge, there are no prior studies estimating the clinically meaningful change in TWSTRS subscores required to determine sample size in clinical trials for subjects with CD. Previous studies have suggested a 9-point change in the *total* TWSTRS score to be a clinically meaningful effect size [26] and a standard deviation of difference in total TWSTRS score from baseline to be 10 [26]. Using these assumptions in a two sample, cross-over design with a two tailed $P = 0.05$ and a 90% power of detecting this difference, we estimated a total sample size of 30 subjects.

Statistical analysis

Scores obtained at the beginning and end of each treatment period, with dronabinol and placebo, were compared using a non-parametric Friedman's analysis of variance (ANOVA) test followed by *post hoc* Dunn's multiple comparison test for all variables analyzed. Due to the small number of subjects, GIS and adverse events are descriptive. Significance was assigned when $P < 0.05$. Statistics were computed with the SPSS 13.0 for Windows and GraphPad Prism 5.02 software.

Results

Forty-one subjects were assessed for eligibility, but only nine were randomized. Due to difficulties with enrollment and loss of supply of active drug, the study was terminated after 2.5 years. Seventeen subjects were excluded; the reason in the majority was an inability to stop driving for the duration of the study. Two subjects dropped out during the study (1 due to adverse effects and 1 was lost to follow up after randomization), leaving 7 patients in the final analysis. Demographics and baseline characteristics of the cohort are presented in Table 1. All patients had received at least one prior botulinum toxin injection. Six out of 7 subjects reached the maximum 15 mg drug dose. One patient required a dose reduction to 7.5 mg in the dronabinol treatment phase due to side-effects, including 'wooziness' and 'lightheadedness'.

There was no significant effect of dronabinol compared to placebo on the primary outcome measure, TWSTRS-A ($F_{(4.23)}$, $n = 7$, $P = 0.237$). In addition there was no significant effect of dronabinol

Table 1
Demographics.

Age mean (Std) (years)	60 (+/− 7)
Gender	9F
Disease Duration mean (std) (years)	16.5 (+/−9)
TWSTRS-A – Severity Median (Range)	16.5 (7–24)
TWSTRS-B Disability Median (Range)	13 (1–22)
TWSTRS-C Pain Median (Range)	11.5 (0–19)
TWSTRS-Total Median (Range)	25.5 (13–54.5)
Visual Analog of Pain	6 (1.5–9.9)

on any of the secondary outcome measures (Total TWSTRS, $P = 0.96$; TWSTRS-B, $P = 0.216$; TWSTRS-C $P = 0.656$; VAP scale $P = 0.273$, all $n = 7$) (Table 2). Three subjects reported minimal improvement after receiving dronabinol, one thought she was slightly worse and three felt there was no change. After placebo, two reported slight improvement (one also experiencing improvement after dronabinol), two reported slight worsening, and 3 no change.

Adverse events were experienced by 8 out of 9 patients. There were no serious adverse events. One subject withdrew from the study during the dronabinol treatment phase due to insomnia and a feeling of her heart racing; these symptoms resolved on discontinuing drug. All adverse events in the remaining 7 subjects occurred during the dronabinol phase of treatment and consisted of lightheadedness, sleepiness, dry mouth, blurred vision, bitter-taste and vertigo and were reported as mild. Two subjects on dronabinol had a fall in systolic drop in blood pressure of more than 15 mm Hg. In one subject this was asymptomatic and the other had the dose reduction as described above. There were no significant weight fluctuations among any of the subjects.

Discussion

The cannabinoid CB1 receptor agonist, dronabinol, was ineffective in reducing CD symptoms over a 3 week treatment period. The drug was reasonably tolerated but this study suggests that cannabinoids may not be useful in the treatment of dystonia. A prior open label study reported that the cannabinoid, cannabidiol was effective in treating five patients with different forms of dystonia [27]. Cannabidiol is the non-psychometric component of *cannabis sativa* and the mechanism of action is poorly understood but may involve 5-HT receptors rather than CB1 receptors thus accounting for the proposed anxiolytic properties of the drug [28] .

There are several possible reasons why no benefit was shown in our study; one factor being that the targeted number of patients estimated in the power calculation ($n = 30$) for a clinically mean-

Table 2
Subject* scores pre and post drug and placebo.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 7	Subject 8	Subject 9
TWSTRS A							
Dronabinol							
Pre	23	9	10	20	10	16	19
Post	25	7	11	22	10	19	19
Placebo							
Pre	24	15	7	22	10	16	18
Post	21	14	10	18	10	18	16
TWSTRS B							
Dronabinol							
Pre	22	6	6	10	3	15	18
Post	18	2	4	8	3	10	15
Placebo							
Pre	20	11	6.5	1	3	17	20
Post	11	14	5.5	7	4	16	14
TWSTRS C							
Dronabinol							
Pre	10	13	5.5	18.25	0	11.25	4.5
Post	14.5	10.25	8.75	12.8	0	11.25	3.75
Placebo							
Pre	12.5	14	2	19	0	11.75	3.75
Post	15.5	12	3.8	18	1.75	13.8	5
TWSTRS total							
Dronabinol							
Pre	55	28	21.5	48.25	13	42.25	41.5
Post	57.5	19.25	23.75	42.8	13	40.75	37.75
Placebo							
Pre	56.5	40	15.5	42	13	44.75	41.75
Post	47.5	40	19.3	43	15.75	47.8	35
VAP							
Dronabinol							
Pre	3	6.5	1.5	9.6	1.75	6	2
Post	3	6.5	1.5	7.7	1.2	5	2
Placebo							
Pre	3	6.45	1.5	9.6	1.75	6	2
Post	3.8	6.5	1.5	10	0.7	6	2
GIC							
Dronabinol	0	0	1	1	−1	1	0
Placebo	0	0	-1	0	−1	1	1

*Only includes 7 subjects who completed entire study.
GIC – Global Impression of Change.
Study Arm A: Subjects 1,4,5.
Study Arm B: Subjects 2,3,6,7.
TWSTRS- Toronto Western Spasmodic Torticollis Rating Scale: TWSTRS-A – Severity; TWSTRS-B – Disability; TWSTRS-C – Pain.
VAP – Visual Analog of Pain.

ingful difference between treatments could not be reached. However, this number is likely to be an overestimate and much larger than is usually required for pilot, phase IIa studies. As a hint of lack of any positive effect, in our study no subject achieved a 9 point (suggested to be a clinically meaningful change) or greater, difference in total TWSTRS score. In addition, the power calculations were based on total TWSTRS scores not subscores i.e. TWSTRS-A, B or C subscores, where smaller changes in outcome may be clinically relevant.

One potential benefit of dronabinol may have been on pain associated with dystonia. In animal studies, cannabinoids produce four classical cannabinomimetic effects including antinociception (analgesia) without respiratory suppression, reduced spontaneous activity, catalepsy and hypothermia [29]. A synthetic buccal spray of *cannabis sativa* extract containing Δ^9THC (2.7 mg) and cannabidiol (2.5 mg) is licensed for neuropathic pain and adjunctive analgesic treatment in advanced cancer. However, in our study, no effect was seen even in individuals with significant pain.

One of the major obstacles to recruitment was the limitation on driving that was required given the uncertainty about possible sedation while on the study drug. However, sedation was only reported by 2 individuals and was mild and did not result in reduced dose or withdrawal from the study; thus clinical trials of cannabinoids in clinical trials could be more lenient with respect to this requirement, allowing easier recruitment. It was possible that by only recruiting subjects for whom driving was not as issue, we could have recruited subjects with more severe CD, and potentially biased the outcome. However, the range of TWSTRS-A scores was between 7 and 24, including a wide variability in baseline severity. The number of individuals participating was too small to perform any subgroup analysis to determine the effect of baseline severity on response.

The relative efficacy of synthetic cannabinoids in stimulation of cannabinoid receptors in the human basal ganglia remains uncertain and so the lack of effect in our study may have been due to inadequate potency at CB1 receptors or dose of this formulation or both. To ensure potency at the CB1 receptor, dronabinol was used in this study rather than nabilone as dronabinol contains Δ^9-THC, a more potent cannabinoid CB1 agonist than the components of nabilone, which is a mixture of Δ^9 THC, cannabinol, cannabidiol and other cannabinoids [30]. Despite this, there was no significant effect on dystonia. CB1 receptor agonists, with higher affinity than Δ^9-THC, are available *in vitro*, however, to date none are available clinically [29,31].

In this study, dose ranges were based on conservative estimates of tolerability and thus it is possible that higher doses could have resulted in improved outcomes. However a placebo controlled case study using Δ^9-(THC) in a subject with musician's dystonia reported improved symptoms using a lower dose of 5 mg/d [32]. Tolerability of dronabinol, 15 mg/d, in our study was good, although most subjects did report some side-effects, particularly lightheadedness, drowsiness and anxiety. It is possible that slower titration over a longer period may have allowed subjects to reach and tolerate higher doses. In support of this, in a single case report, a subject with blepharospasm responded after several weeks to 25 mg daily of dronabinol, but not to lower doses [33]. The relatively short duration of treatment (3 weeks) was used for practical purposes and safety concerns. However, it is likely that in treating dystonia, a much longer time frame is required. Thus, in patients treated for dystonia using anticholinergic drugs and those who undergo deep brain stimulation for dystonia, improvements can be delayed by several months, suggesting longer exposure to higher doses of cannabinoids may be necessary before conclusions can be made.

There remains much medical and public interest in the use of cannabinoids in the treatment of chronic neurological disorders. Many earlier anecdotal reports showed potential for marijuana (*cannabis sativa)* to alleviate a range of medical symptoms. Several recent studies have demonstrated potential for synthetic cannabinoids in disorders such as multiple sclerosis [34,35] and pain [34,36]. There remain much uncertainty and controversy surrounding the short term and long term medical issues associated with synthetic cannabinoids, as to date, most evidence of the adverse effects of cannabinoids relates to the effects of smoking *cannabis sativa* [37]. It is possible that oral synthetic cannabinoids will not have the same side effects as *cannabis sativa*, as a recent study with 12 months of follow up, demonstrated oral cannabinoids were well tolerated [38]. Finally, tolerance to benefit from long term cannabinoid use is a theoretical issue and needs clarification with further randomized controlled trials.

Conclusions

Idiopathic dystonia remains poorly understood and inadequately treated. Cannabinoids have been suggested as a treatment for dystonia due to potential action on CB1 receptors within the basal ganglia. The synthetic cannabinoid, dronabinol, failed to show any effect in 9 subjects with cervical dystonia. However, due to difficulties with enrollment, the study was underpowered and therefore, results must be interpreted with caution. If further studies are attempted, a longer exposure to higher doses should be considered.

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