

Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis

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Keywords:

cannabis-based medicine, multiple sclerosis, Sativex, spasticity

Received 6 April 2006

Accepted 18 August 2006

Symptoms relating to spasticity are common in multiple sclerosis (MS) and can be difficult to treat. We have investigated the efficacy, safety and tolerability of a standardized oromucosal whole plant cannabis-based medicine (CBM) containing Δ -9 tetrahydrocannabinol (THC) and cannabidiol (CBD), upon spasticity in MS. A total of 189 subjects with definite MS and spasticity were randomized to receive daily doses of active preparation ($n = 124$) or placebo ($n = 65$) in a double blind study over 6 weeks. The primary endpoint was the change in a daily subject-recorded Numerical Rating Scale of spasticity. Secondary endpoints included a measure of spasticity (Ashworth Score) and a subjective measure of spasm. The primary efficacy analysis on the intention to treat (ITT) population ($n = 184$) showed the active preparation to be significantly superior ($P = 0.048$). Secondary efficacy measures were all in favour of active preparation but did not achieve statistical significance. The responder analysis favoured active preparation, 40% of subjects achieved >30% benefit ($P = 0.014$). Eight withdrawals were attributed to adverse events (AEs); six were on active preparation and two on placebo. We conclude that this CBM may represent a useful new agent for treatment of the symptomatic relief of spasticity in MS.

Introduction

Multiple sclerosis (MS) is the leading cause of neurological disability amongst young and middle-aged peoples in northern industrialized nations [1]. Spasticity remains one of its most recalcitrant symptoms and is said to be present in up to 84% of cases [2]. Systematic review of available muscle relaxant treatments have shown that the overall benefit is small, tolerability has restricted their potential and more effective treatments are needed [3].

Spasticity is difficult to measure and has no single defining feature. It is part of the upper motor neurone

syndrome which includes hyper-reflexia, increased tone (resistance to passive movement), muscle weakness, loss of dexterity and leads to abnormal posture, fatigability, pain and muscle spasms.

Cannabis has long been proposed as an antispasmodic and muscle relaxant [4]. Evidence from surveys suggests that many people with MS use cannabis for symptom relief [5]. The therapeutic effects of cannabis-based medicines (CBM) have been investigated in several published clinical studies assessing effects on spasticity, sleep neuropathic pain, lower urinary tract impairments and other symptoms in MS [7–11]. There is a strong pharmacological rationale for proposing that a CB1 cannabinoid receptor agonist may have therapeutic effects in the treatment of spasticity [12].

The study described here examines the efficacy, benefits and adverse effects of a specific CBM (Sativex[®]) in subjects with spasticity due to MS in a 6 week, multicentre, phase III, double blind, randomized, parallel group study.

Methods

Subjects over 18 years of age with a documented diagnosis of MS and stable disease for at least 3 months before study entry were studied. They were required to have significant spasticity in at least two muscle groups

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with an Ashworth score [13] of two or more; have failed to gain adequate relief using current therapy; be on stable treatment for at least 30 days before entry and during the study. Effective contraception was required for subjects of child bearing potential. Use of cannabis or cannabinoids (Marinol[®], Solvay Pharmaceuticals, Marietta, GA, USA or nabilone) was prohibited during the study and for at least 7 days before visit 1.

Exclusion criteria included psychosis or severe psychiatric disorder other than depression, known alcohol or substance abuse, severe cardiovascular disorder including poorly controlled hypertension, history of seizures, pregnancy or lactation sensitivity to cannabinoids, and planned travel abroad during the study. Approval was obtained from independent ethics committees. All subjects gave informed consent before their enrolment. The first subject entered the study in April 2002, and the last subject completed the study in March 2004.

The treatment

Study treatment was a highly standardized oromucosal spray (Sativex) developed by GW Pharmaceuticals under licence of the British Home Office. It is extracted from cloned cannabis chemovars grown under environmentally controlled glasshouse conditions in organic media, in accordance with Good Agricultural Practice [14,15]. Each 100 μ l actuation yields 2.7 mg of delta-9-tetrahydrocannabinol (THC) and 2.5 mg of cannabidiol (CBD) in a solution of 50:50 ethanol:propylene glycol. This preparation has an onset of activity within 15–40 min allowing ready dose titration and the pharmacokinetics and pharmacodynamics have been described previously [16]. The control (placebo) preparation was identically flavoured incipient to reduce the risk of unblinding.

Study design

This study was a randomized, parallel group, double blind, multi-centre study run in eight centres in the UK and four centres in Romania conducted in compliance with Good Clinical Practice.

The primary outcome measure was the change from baseline in the severity of spasticity based on a daily diary assessment by the subject on a 0–10 numerical rating scale (NRS). Secondary outcome measures included change from baseline in; a composite score of the Ashworth Scale [13] and Motricity Index [17,18] in muscles affected by spasticity, mean daily spasm scores (five point spasm frequency score) and the patients global impression of change (PGIC) in their disease (seven point scale, very much improved to very much

worse). The Ashworth Scale is measured by an observer stretching the selected muscle group passively and scoring the resistance to movement, and Motricity Index is a validated measure of muscle power assessing pinch grip, elbow flexion, shoulder abduction, ankle dorsiflexion, knee extension and hip flexion. Adverse events were collected throughout the study and compared between treatment groups.

Originally, the primary outcome measure was the Ashworth Scale but publication of the CAMS study [6] provided confirmation of its lack of reliability and sensitivity to measure significant functional change in spasticity, in agreement with recent systematic reviews [1,3]. During patient recruitment an application was made to the independent ethics committees to reorder the outcome data, NRS became the primary measure of efficacy. This amendment was finalized 2 months before the last patient was recruited for the study. Data lock and analysis occurred 4 months after implementation of the amendment with full ethical approval.

Eligible subjects were instructed to complete the 11-point NRS for spasticity, intoxication and spasm frequency score in daily diary throughout the study. Subjects returned after 2 weeks (visit 2), for examination of limb spasticity using the Ashworth protocol. Muscle groups with Ashworth scores of two or greater were selected for subsequent monitoring.

Subjects were randomized to CBM or placebo in a 2:1 ratio by a balanced schedule design for each centre. Subjects were instructed to titrate their daily dose steadily as required over 2 weeks, to a maximum of 48 sprays per day. Concomitant medications and therapies were maintained during the study course.

At visit 3, 2-weeks later, adverse events, concomitant medication use, spasticity in affected muscles and diary entries were assessed. Finally, after 6 weeks of study medication (study end or early withdrawal), affected limbs were re-assessed, along with diary entries, PGIC, ECG, vital signs, blood chemistry, haematology, urinalysis and pregnancy test where appropriate.

Statistical analysis

Data entry and statistical analysis were carried out by an independent Contract Research Organization (Parxel International Ltd, Uxbridge, UK). NRS of spasticity, Ashworth scores, Motricity Index and the other diary card variables were analysed and compared using analysis of covariance (ANCOVA) with baseline severity as the covariate. The resulting residuals from the analysis were examined for evidence of non-normality before presenting the parametric results. NRS spasticity measures were assessed by comparing the mean of the last 7 days of baseline data to mean on-treatment

values computed weekly during the study. A responder analysis was conducted counting the number of people who experienced a reduction in NRS spasticity score by 30% and 50% or more of their initial score. PGIC was assessed via frequency tables comparing groups with Fisher's Exact Test. A two-sided significance test was employed in all comparisons at the 5% level of significance, and calculation of 95% confidence intervals of difference between treatments. The primary analysis was performed on the intention-to-treat (ITT) population, defined as all randomized subjects receiving at least one dose of study medication with recorded post-baseline efficacy data. AEs were coded according to *Medical Dictionary for Regulatory Activities (MedDRA)*.

Results

Efficacy

Of 226 subjects entering the study, 37 failed screening and 189 subjects were randomized in a 2:1 ratio: 124 to CBM, and 65 to placebo (Fig 1). The ITT population totalled 184 subjects (120 CBM:64 placebo) and the safety population totalled 189 subjects.

Study groups (Table 1) were comparable with no statistically significant differences. The mean duration of MS was 12.6 years. In the CBM cohort, 117 (94.4%) had at least one continuing medication vs. 56 (86.2%) of controls. A stable pattern of study medication dosing was established within 2 weeks dosing patterns are depicted in Table 2.

For the primary efficacy measure, the adjusted mean change in 11-point NRS spasticity scores for the CBM group at the end of treatment showed a reduction of 1.18 points from a mean baseline period score of 5.49 points. For the corresponding period, the placebo group showed an adjusted mean decrease of 0.63 points from a mean baseline period score of 5.39 points. The estimated treatment difference of 0.52 points, in favour of the CBM group was statistically significant ($P = 0.048$; 95% CI: -1.029 , -0.004 points) (Fig. 2).

The responder analysis showed that in the CBM group 48 (40.0%) subjects showed a $\geq 30\%$ reduction in NRS spasticity over the study as compared 14 (21.9%) on placebo (difference in favour of CBM = 18.1%; 95% CI: 4.73, 31.52; $P = 0.014$). Twenty-one (17.5%) of CBM vs. six (9.4%) of placebo subjects experienced a $\geq 50\%$ reduction in NRS spasticity (difference in favour of CBM = 8.1%; 95% CI: -1.73 , 17.98; $P = 0.189$). At all thresholds over a 30% improvement in spasticity score, the odds ratio in favour of CBM exceeded two (Fig. 3).

For subjects who reported previous exposure to cannabis, the adjusted mean change in 11-point NRS for spasticity, for the CBM treatment group, showed a decrease of 1.08 points from a mean baseline period score of 5.52. For the corresponding period, the placebo group showed an adjusted mean decrease of 0.30 points from a mean baseline period score of 5.16 points ($P = 0.046$; 95% CI -1.025 , -0.008 points). There was no statistical evidence of a treatment by previous cannabis use interaction ($P = 0.8$).

Sixty-six (57%) subjects on active treatment rated global impression of change as improved, compared with 31 (48%) controls. Table 2 shows remaining results.

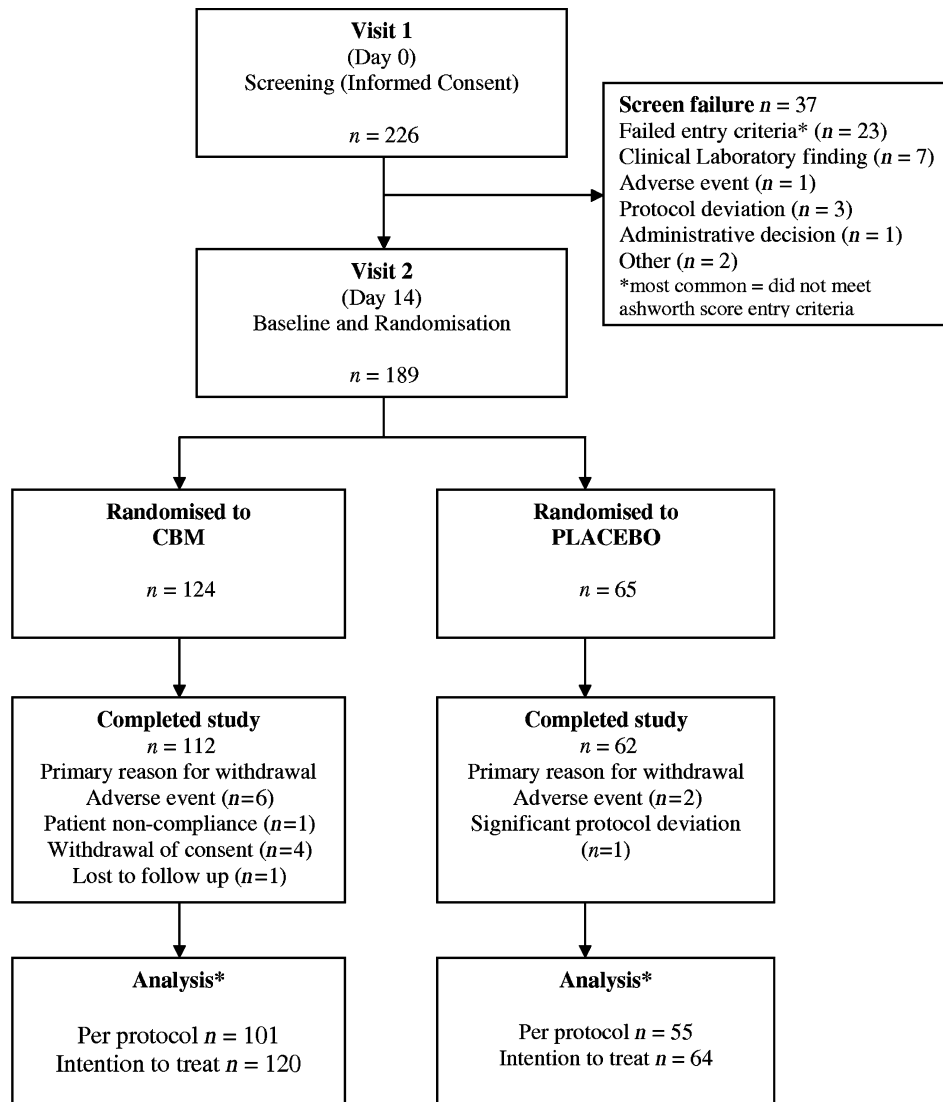
Safety

Treatment emergent AEs in the safety population occurred in 102 (82%) of subjects on CBM and 46 (71%) on placebo. There were a few notable differences in the pattern of AEs between groups, except for CNS effects (dizziness, impaired balance, disturbance in attention and blurred vision), which were more common in the CBM group. The majority AEs were of mild or moderate severity (non-serious AEs occurring in four or more subjects see Table 3). There were seven serious AEs, four in the CBM group (3.2%) and three in the placebo group (4.6%). Only one was considered to be possibly related to treatment, a case of vomiting in a subject receiving CBM.

Only six (4.8%) subjects on CBM and two (3.1%) on placebo withdrew due to AEs. There were no deaths. No significant attributable laboratory, haematological, urological or ECG changes were noted. Vital signs did not vary significantly between groups neither during initial dosing nor during stable administration. Mean Intoxication NRS Scores remained below two for both groups during initial dosing (0, no intoxication; 10, extreme intoxication).

Discussion

This study has shown that over a 6-week period of use subjects rated CBM significantly more effective than placebo in relieving their spasticity. The secondary outcomes did not achieve statistical significance but were all in favour of CBM. There was an increase in muscle power in the legs suggesting that reduction in spasticity was not gained at the cost of increasing weakness [19,20] a problem associated with currently available oral antispasticity medication. The reordering of endpoints during the study raised no methodological concern as it was conducted during study recruitment before any unblinding and data analysis.



*Five patients who took CBM had no post-baseline efficacy data and therefore could not be included in the IIT population.

Figure 1 Study schema.

There have been several studies which have examined the effect of various CBMs in MS [8–10,21,22]. Zajicek *et al.* published the results of a placebo controlled comparison of an oral extract of cannabis and the synthetic cannabinoid THC in 630 patients with MS [6,23]. The primary efficacy endpoint of this study, the Ashworth Scale, did not demonstrate a beneficial effect on spasticity. The results were significantly in favour of both cannabis extract and THC for the patient recorded symptoms of spasticity and pain. This 12-month follow-up study [7] provided evidence for a longer-term treatment effect of cannabinoids. The Ashworth results just reached statistical significance with far greater benefit reflected by the patient rated spasticity scale.

This study was double blind. No attempt was made to assess the effectiveness of this whilst patients were taking the study medication, but the analysis plan specified that the treatment effect size would be examined taking prior use of medicinal cannabis into account. There was no correlation between treatment effect or the commonest side effect dizziness and previous exposure to cannabis. The possibility of bias from unblinding due to treatment side effects cannot be discounted.

The majority of AEs in this study were mild or moderate in severity, and the low rate of subject withdrawal from the study provides good evidence of tolerability. There were very few serious AEs. In general,

Table 1 Baseline subject characteristics

	Number of subjects (%)		
	CBM	Placebo	Total
Gender			
Male	44 (35.5)	31 (47.7)	75 (39.7)
Female	80 (64.5)	34 (52.3)	114 (60.3)
Previous cannabis use	52 (41.9)	27 (41.5)	79 (41.8)
	Mean (SD)		
Age	49.7 years (10.2)	47.8 years (9.5)	49.1 (9.9)
Duration of MS	13.6 years (8.6)	12.2 years (7.7)	

AEs fell into one of two categories, either intoxication-like reactions or application site reactions. Both of these tended to occur in the first weeks of the study, and neither was associated with significant morbidity. AEs in the category of an intoxication-like reaction were more common in the subjects in the CBM group. The low rate of subject withdrawal due to AEs may seem surprising given that the dose of THC, the psychoactive element of cannabis, was being taken in mean daily

doses in excess of 25 mg, considerably more than was given in other published studies. This good tolerability may be related to the method of administration, where relatively small doses could be taken at a time. It may be related to the route of administration, which largely avoids the gastro-intestinal tract, or it may be related to the presence of other cannabinoids and other plant components. There is evidence that suggests CBD may modify some of the psychoactive effects of THC, so that THC as part of a cannabis extract becomes better tolerated than THC as a single molecule [24].

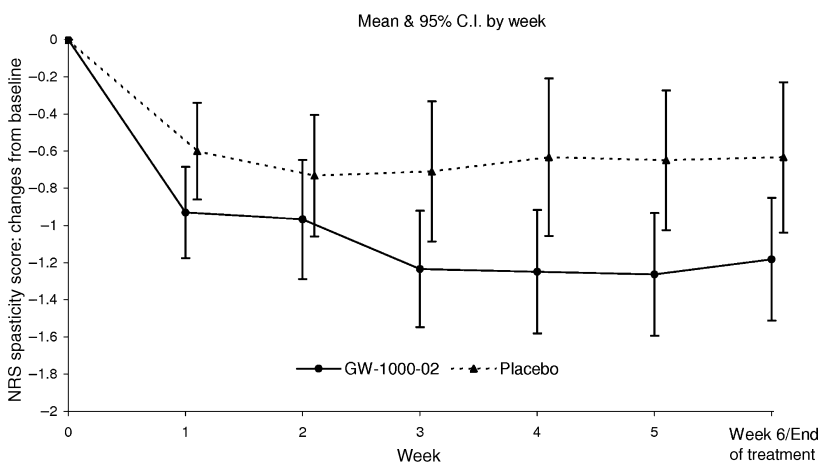
One criticism of this study is the use of a patient-centred, self-report primary outcome measure, the numerical rating scale (NRS) rather than an observer rated scale. We would defend this strongly. In clinical practice objective assessment of spasticity is rarely attempted, most physicians basing clinical decision-making on the weight of evidence provided by self-report of the patient and sometimes the carer [2,13,25]. There is increasing acceptance that a patient reported outcome measure is appropriate for spasticity. The 11-point NRS was used in an attempt to capture what

Table 2 Secondary endpoint and dosing results

Measure	Change in mean from baseline to visit 4		Difference (95% CI)	SE	P-value
	CBM	Placebo			
Ashworth	-0.64	-0.53	0.11 (-0.29, 0.07)	0.09	0.218
Spasm frequency	-0.39	-0.22	0.17 (-0.39, 0.06)	0.11	0.141
Motricity Index (legs)	5.71	1.85	3.86 (-0.06, 7.78)	1.99	0.054
Motricity Index (arms*)	3.91	2.61	1.30 (-7.47, 10.07)	4.33	0.766

Overall dosing of study medication, mean number of sprays per day

Mean (SD)	Median	Lower quartile	Upper quartile	Mean (SD)	Median	Lower quartile	Upper quartile
9.4 (6.4)	6.8	4.8	12.9	14.7 (8.4)	12.6	8.4	19.7

**Figure 2** Change in NRS spasticity score from baseline with time for the CBM (GW-1000-02) and placebo patient groups.

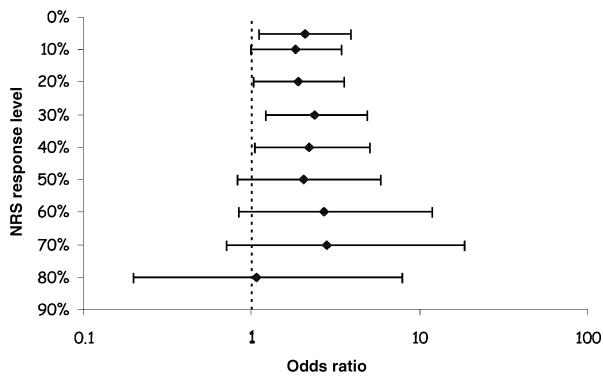


Figure 3 Responder analysis. The percentage response level is represented on the vertical axis and the odds ratio on the horizontal axis. When the 95% confidence interval lower bound exceeds 1, the result is statistically significant in favour of CBM. At all response rates from 30% to 70% the odds ratio in favour of CBM exceeds 2.

Table 3 Treatment emergent adverse events compared with treatment related adverse events experienced by greater than four subjects receiving CBM compared with placebo

Preferred term	All causality number and percentage of subjects	
	CBM (<i>n</i> = 124)	Placebo (<i>n</i> = 65)
Dizziness	40 (32.3)	7 (10.8)
Fatigue	13 (10.5)	4 (6.2)
Urinary tract infection	13 (10.5)	6 (9.2)
Dry mouth	11 (8.9)	4 (6.2)
Balance impaired	9 (7.3)	1 (1.5)
Nausea	9 (7.3)	4 (6.2)
Headache	8 (6.5)	4 (6.2)
Diarrhoea	7 (5.6)	2 (3.1)
Oral pain	6 (4.8)	7 (10.8)
Somnolence	6 (4.8)	1 (1.5)
Confusion	6 (4.8)	2 (3.1)
Depressed mood	6 (4.8)	0
Constipation	5 (4.0)	1 (1.5)
Disorientation	5 (4.0)	1 (1.5)
Dysgeusia	5 (4.0)	1 (1.5)
Disturbance in attention	4 (3.2)	0
Euphoric mood	4 (3.2)	2 (3.1)
Vision blurred	4 (3.2)	0
Weakness	4 (3.2)	1 (1.5)
Pain in limb	4 (3.2)	1 (1.5)

spasticity was like over a 24-h period, rather than at a single point in time, in an attempt to reflect the overall patient's daily experience of their spasticity [3].

The NRS is accepted as a standard instrument in the clinical assessment of pain, a symptom whose impact in patients with MS may be seen as similar to that of spasticity. It fulfils published criteria for the validity of a qualitative scale [26]. In the pain context, it has been proposed that an improvement of around 30% from

baseline equates to a clinically meaningful reduction [27]. It is uncertain how much this relates to spasticity, and the MS Society have noted 'it may be all too easy to dismiss some of the small but significant impacts these drugs could have without considering the perspective of people affected by the condition' [28]. Small improvements in the patients experience may lead to large changes in quality of life. In this study, 40% of the ITT population achieved >30% improvement from baseline. It is notable that this improvement was gained over and above the concomitant anti-spasticity medication being taken by the subjects.

There is a compelling neuropharmacological rationale to support the use of CBM in the relief of spasticity in MS with evidence from both anatomical human and animal studies [29–31].

The results of this study provide us with cautious optimism that CBM can improve the symptoms of spasticity in MS sufferers. The ideal objective measure of spasticity does not exist. Using the NRS as in pain research appears to be a reasonable compromise. The goal for people with MS is to improve function and quality of life. The challenge for researchers is to develop simple, reliable and robust measures that capture change in function and quality of life and link them to changes in impairments like spasticity.

Acknowledgements

We thank all the patients who took part in this study. We acknowledge the assistance provided by staff at all the investigator centres.

Competing interests

This study was sponsored and fully funded by GW Pharma Ltd. Investigators received research grants from GW Pharma Ltd to cover the costs of the study. CC and SR have had expenses paid by Bayer Healthcare to attend relevant conferences and PD and CC have acted as clinical experts for GW Pharma Ltd.

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