Oreja-Guevara et al., Clin Exp Pharmacol 2015, 5:5
DOI: 10.4172/2161-1459.1000184

Clinical & Experimental Pharmacology

Research Article Open Access

Observational Safety Study of THC:CBD Oromucosal Spray (Sativex) in Multiple Sclerosis Patients with Spasticity

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Abstract

Background: Subsequent to introduction in June 2010 in the United Kingdom and Spain of tetrahydrocannabinol (THC) : cannabidiol (CBD) oromucosal spray (Sativex®) for management of multiple sclerosis (MS) spasticity, and as part of a wider initiative to address British health authority requirements for post-marketing surveillance to identify possible short- and long-term risks associated with its use as a condition of marketing authorization, studies were undertaken to evaluate the safety of THC:CBD spray under clinical practice conditions.

Methods: This prospective, observational, multicentre study reports on 205 patients with treatment-resistant MS spasticity who were prescribed THC:CBD spray as add-on therapy to existing antispasticity medications at 13 specialist MS centres across Spain. Safety evaluations were performed after 6 and 12 months' exposure to THC:CBD spray.

Results: Add-on THC:CBD spray was well tolerated during up to 12 months' exposure. No new safety signals emerged and THC:CBD spray was not associated with any clinically-relevant occurrence of adverse events of special interest with cannabinoid-based medications such as falls requiring medical attention, psychiatric or psychotic symptoms, memory impairment, changes in driving ability, addiction or abuse. After 6 months' and 12 months' exposure, treating physicians considered that 139 patients (68% of original cohort) and 124 patients (60.5% of original cohort), respectively, were deriving sufficient anti-spasticity benefit from THC:CBD spray to warrant continued treatment. The mean dosage of THC:CBD spray (6.6 sprays/day) and carer requirements (~14.5 hours/day) remained stable throughout the study.

Conclusions: THC:CBD spray as add-on therapy showed good tolerability and sustained anti-spasticity benefit in a relevant proportion (60.5%) of Spanish patients with MS-related spasticity treated for up to 12 months in everyday clinical practice.

Keywords: Multiple sclerosis; Pharmaco-epidemiology; Safety; Spain; Spasticity; THC:CBD spray

Introduction

Spasticity is a common and highly distressing symptom of multiple sclerosis (MS) that typically adds to the burden of disease [1-2]. Muscle stiffness, spasms and pain can limit mobility and interfere with activities of daily living. Associated symptoms such as disturbed sleep, depression and loss of personal independence combine to have a profoundly negative impact on patient's quality of life.

A number of medications are available to treat spasticity but the evidence base for their use is weak and the benefits are generally modest [2-4]. Evidence-based MS spasticity management algorithms are becoming available to guide clinical decision-making [5], as it is not uncommon for patients with MS spasticity to seek unproven alternative solutions for symptomatic relief. The known biology of the endocannabinoid system supports the hypothesis that cannabis derivatives can relieve spasticity and other symptoms of MS [6-8].

Sativex® oromucosal spray is a first-in-class endocannabinoid system modulator approved in a growing number of countries for management of treatment-resistant MS spasticity [9]. The main active ingredients, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) formulated in a near 1:1 ratio, are extracted from selected chemotypes of the *Cannabis sativa* plant and may have complementary pharmacological properties [7]. THC acts as a partial agonist of the cannabinoid 1 (CB_1) receptor, which plays a relevant role in the modulation of spasticity and spasms [8]. CBD has a different profile of cannabinoid receptor activity and has been shown to ameliorate the anxiogenic, psychoactive and sedative effects of THC [9-11].

THC:CBD spray is indicated for symptomatic improvement in patients with moderate to severe MS spasticity who have not responded adequately to other antispasticity medications and who demonstrate a clinically significant improvement in spasticity-related symptoms during an initial trial of therapy. Administered as an oromucosal spray, THC:CBD spray provides dosing flexibility such that patients can self-manage the variable nature of their spasticity. Randomized clinical trials have demonstrated that THC:CBD spray is effective and well tolerated in MS patients with refractory spasticity who responds to treatment [12-15].

In June 2010, THC:CBD oromucosal spray received marketing approval in the United Kingdom (UK) and Spain. As a condition of authorisation, British health authorities requested that post-marketing evaluation be undertaken to identify possible short- and long-term risks associated with its use under clinical practice conditions. By means of structured questions, particular regard was to be given to the potential for adverse events of special interest with cannabinoid-based medications.

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Received: July 03, 2015; **Accepted:** July 31, 2015; **Published:** August 07, 2015

Citation: Oreja-Guevara C, Casanova B, Ordás CM, Vila C, Asensio D, (2015) Observational Safety Study of THC:CBD Oromucosal Spray (Sativex) in Multiple Sclerosis Patients with Spasticity. Clin Exp Pharmacol 5: 184. doi:10.4172/2161-1459.1000184

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A patient registry was established in the UK (and subsequently in Germany) for post-marketing surveillance of THC:CBD spray. All UK physicians who prescribe THC:CBD spray are invited to participate in the Registry. Every 6 months prescribers are asked to complete a Case Record Form on patients who have received at least one prescription of THC:CBD spray. Interim results of the retrospective registry study have been reported [16].

Although Spanish health authorities did not require a patient registry *per se,* it was recommended nonetheless that safety data be collected. A study was implemented with methodology similar to that of the UK Registry study in terms of key safety data to be collected, but with a prospective design and conducted in selected MS centres. The objective of the study was to identify, characterise and quantify potential risks associated with use of THC:CBD spray by systematically collecting information about all suspected adverse drug reactions that occurred in patients in the first 12 months from the start of treatment under usual clinical practice conditions in Spain.

Methods

Patients and methods

This prospective, observational, multicentre, pharmaco-epidemiological study was undertaken subsequent to approval of THC:CBD spray by the Spanish health authorities. The study involved 13 specialised MS centres located throughout Spain that had been selected specifically for their larger patient populations.

Individuals eligible for entry were male and female patients ≥ 18 years with moderate or severe MS-related spasticity who had not responded adequately to other antispasticity medications and who were prescribed THC (2.7 mg per spray [100 µl]) / CBD (2.5 mg per spray [100 µl] oromucosal spray according to approved conditions of use in the Summary of Product Characteristics [17]. THC:CBD spray was to be prescribed according to physicians' usual clinical practice prior to, and independently of, a patient's potential participation in the study.

To minimise selection bias, patients prescribed add-on THC:CBD spray at each centre were invited to participate in the study in a consecutive manner (i.e. one after the other). At the treating physician's discretion, patients who did not meet study requirements, or those with a medical or psychological disorder that would limit their ability to understand questions and complete the questionnaires, were excluded from an invitation to participate.

The study design was evaluated and approved by the ethics committee of the Hospital Universitario La Paz in Madrid in accordance with international standards for conduct of epidemiological studies contained in the International Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences-CIOMS-Geneva, 1991) and recommendations of the Spanish Society of Epidemiology on revision of ethical aspects of epidemiological research. The study was conducted in accordance with principles of the Declaration of Helsinki and in compliance with standards of Good Clinical Practice, as described in the International Conference for Harmonisation Guidelines for Good Clinical Practice 1996.

Patients provided written informed consent to participate in the study.

Data collection

Treatment evolution data were sourced from relevant information collected during routine consultations by means of a standardised electronic case report form (e-CRF) agreed with British and Spanish health agencies prior to study start. Participating physicians were trained to collect and submit data electronically to the clinical research organisation for compilation and analysis. The observation period consisted of three evaluation timepoints: baseline, 6 months and 12 months. Data analysis was scheduled after 6 and 12 months' exposure to THC:CBD spray (or before if the patient discontinued treatment).

The electronic data capture system prompted investigators to enquire about general tolerability with the patient at each clinic visit. Patients could report more than one adverse event at each visit. In addition, structured questioning was used to evaluate the potential of THC:CBD spray for:

Addiction: Abuse and/or misuse for illegal purposes

Long-term psychiatric effects: Including suicidal tendencies and psychosis

Mood changes / psychological effects: (such as confusion or disorientation)

Memory impairment

Effects on driving ability

Falls

To minimise errors in data capture, each field in the e-CRF had predefined limits. Open fields were included for recording of serious adverse events.

At both the 6-month and 12- month evaluations, patients' medical records were reviewed to collect information about visits during the previous 6-month period for other reasons (e.g. other visits to the MS unit, emergency room visits, visits to other specialists) in order to capture any possible adverse events reflected in these visits.

Statistical analysis

The safety analysis group included all patients enrolled in the study (n=205) and was the group used for all statistical summaries. Descriptive statistical parameters were used to summarise demographics, clinical characteristics and patient history. Continuous variables were summarised by the number of non-missing values (number [n], mean, standard deviation, median, minimum and maximum); and categorical variables were summarised by the number and percentage of patients in each category.

Results

Patient disposition

Between July 2011 and December 2012, 207 patients with moderate to severe treatment-resistant MS spasticity were recruited into the study at 13 specialist MS centres across Spain (mean 14 patients/centre, range 3-31). Two patients did not attend at least one follow-up visit and were excluded from analyses. Of the 205 evaluable patients, 63 (30.7%) had at least one follow-up evaluation (either at 6 or 12 months) and 142 (69.3%) had two follow-up evaluations, one each at 6-12-months. A total of 73 patients discontinued THC:CBD spray permanently during the observation period: 62 patients before the 6-month evaluation and 11 patients between the 6 and 12-month evaluations. The most common reasons for discontinuation in the first 6 months of treatment were lack of tolerability/adverse events (n=29), lack of effectiveness (n=22), lack of tolerability + lack of effectiveness (n=9) and other/not specified (n=2). Four patients were lost to follow-up.

Demographic and clinical characteristics

The demographic (stratified by response) and clinical characteristics of patients at baseline and after 6 and 12 months' exposure to THC:CBD spray are summarised in Table 1.

At baseline, patients had a mean age of 48.6 (± 9.7) years and 62% of the population were female. No age or gender differences were observed in terms of response to THC:CBD spray.

After 6 months' exposure, treating physicians considered that 139 patients (68% of the cohort) were deriving sufficient clinical benefit from THC:CBD spray to continue with treatment; the corresponding figure after 12 months' exposure was 124 patients (60.5% of the cohort).

At baseline, half the patient sample (51%) reported requiring a carer and this proportion remained relatively constant after 6 (47.5%) and 12 (49.7%) months' exposure. Likewise, the mean number of carer hours required per day remained steady throughout the study: 14.0 hours at baseline; 14.4 hours at 6 months; and 14.9 hours at 12 months.

The mean THC:CBD dosage remained stable throughout the observation period; a mean dose of 6.6 sprays/day (range: 1-14 sprays/day) was recorded after both 6 and 12 months' exposure.

Concomitant medications

At baseline, the majority of patients (n=174, 85% of the cohort) had been receiving at least one other stable (>3 months) medication for MS and/or MS spasticity prior to the addition of THC:CBD spray, predominantly baclofen (n=113), tizanidine (n=46), pregabalin (n=19) or gabapentin (n=18). Approximately half this group were receiving MS disease modifiers: beta-interferons (19.0%), natalizumab (12.6%), glatiramer acetate (9.2%), fingolimod (3.4%) or methotrexate (1.7%). Approximately half of all patients (n=100, 49%) were taking various other medications, most commonly omeprazole (n=14), for comorbid conditions.

Apart from the introduction of THC:CBD spray, use of medications for MS/MS spasticity or other conditions was stable in 81% of patients after 6 months' exposure and in 89% of patients after 12 months' exposure. Among patients with changes to their antispasticity medications, some had doses of concomitant medications decreased and others had new medications introduced, with no clear trend in either direction.

Tolerability/Adverse Events

In total, 57 adverse events of mild (72%), moderate (16%) or severe (12%) intensity were reported by 41 patients (20% of the cohort) during the 12-month observation period. About two-thirds of these events (n=40) had a suspected causal association with THC:CBD spray and involved mainly the gastrointestinal (diarrhoea 6, oral mucosa 3), nervous (dizziness 3, somnolence 2) and psychiatric (depression 3, confusion 2) system organ classes (Table 2). No new safety signals were identified relative to adverse events reported in placebo-controlled clinical trials [17] and the incidence of adverse events decreased over time. Actions taken with THC:CBD spray after suspicion of adverse events (related or not) were treatment withdrawal (60% of cases), no change of dose (21%), treatment interruption and re-introduction (12%) or dose reduction (7%). Full recovery was reported for 43 events (75% of patients); 8 events (14%) remained unresolved at the time of analysis.

Serious adverse events were recorded in 8 patients; of these, two events (<1% of sample, headache in 1 patient and ambulation disturbance/polyuria in 1 patient) were suspected of having a causal relationship with THC:CBD spray. Three deaths occurred during the observation period: two patients had multiple related adverse events (aspiration pneumonia, respiratory failure, acute pulmonary edema, congestive heart failure [n=1]; infectious sepsis, bacteraemia, respiratory failure [n=1]) and a third patient had heart failure. None of the deaths was considered by the treating physician to be related to use of THC:CBD spray.

Adverse events of special interest

With regard to adverse events of special interest (Table 3), two falls occurred, both of which were rated as mild by investigators. No cases were recorded of a patient seeking medical attention because of injury caused by a fall. There were no cases of suicidal thoughts or suicide attempts throughout the entire observation period. Relevant psychiatric/psychotic disorders reported in 5 patients included 4 cases of mild depressive syndrome (3 after 6 months' exposure and 1 after 12 months' exposure) and 1 case of moderate psychotropic effects after 12 months' exposure. Among the 77 still-driving patients with 6 months' exposure to THC:CBD spray, 5 reported improvement, 71 reported no change, and 1 patient reported loss in ability to drive. Among the 57 still-driving patients with 12 months' exposure to THC:CBD spray, 2 reported improvement and 55 patients reported no change in ability to drive.

Discussion

In this prospective, observational, multicentre, pharmaco-epidemiological study, information was systematically collected about all suspected adverse drug reactions that occurred in patients with moderate to severe resistant MS spasticity (n=205) in the first 12 months of treatment with add-on THC:CBD spray under usual clinical practice conditions in Spain. Similarities in demographic and clinical characteristics between the patient sample and those reported in a large survey of Spanish patients with MS spasticity [18] indicated that the population was representative. THC:CBD spray was added to existing antispasticity medications in 85% of cases, confirming treatment-

	Baseline (n=205)	**6 months' exposure (n=204)**		**12 months' exposure (n=143)**	
		With benefit (n=139)	Without benefit (n=59)	With benefit (n=124)	Without benefit (n=13)
Mean age, years ± SD	48.6 ± 9.7	49.2 ± 10.1	47.0 ± 9.1	49.5 ± 10.2	48.7 ± 7.1
Male (%): Female (%)	78 (38) : 127 (62)	55 (40) : 84 (60)	21 (36) : 38 (64)	46 (37) : 78 (63)	4 (31) : 9 (69)
	Baseline (n=205)	**6 months' exposure (n=204)**		**12 months' exposure (n=143)**	
Need for carer	105 (51.2%)	97 (47.5%)		71 (49.7%)	
Mean carer hours/day	14.0 (± 8.7)	14.4 (± 8.9)		14.9 (± 8.3)	
THC:CBD spray dose (sprays/day)	NA	6.6 (± 2.9)		6.6 (± 2.8)	

Table 1: Demographic and clinical characteristics of patients with moderate to severe treatment-resistant multiple sclerosis-related spasticity prescribed add-on THC:CBD oromucosal spray.

Adverse event	After 6 months' exposure (n=204)	After 12 months' exposure (n=143)
Gastrointestinal disorders (n=12)		
Dental caries		1
Diarrhoea	6	
Mouth dryness	1	
Oral aphthae	1	1
Unpleasant taste	1	
Nausea	1	
General disorders (n=3)		
Ambulation disturbance	1	
Generalised weakness	1	1
Infections and infestations (n=1)		
Infectious gastroenteritis	1	
Injury, poisoning, procedural complications (n=2)		
Fall/falls	1	1
Nervous system disorders (n=15)		
Cognitive impairment		1
Difficulty concentrating	2	
Dizziness	3	
Headache	1	1
Short-term memory loss	1	
Mental dullness	1	
Ophthalmoplegic migraine	1	
Sleep paralysis	1	
Somnolence	2	
Stunned	1	
Psychiatric disorders (n=10)		
Anxiety related to missed dose		1
Confusional state	1	
Confusional syndrome	1	
Depressive syndrome	3	
Episode of disorientation		1
Mood change/disinhibition	1	
Psychotropic effect	1	
Quick thinking		1
Renal and urinary disorders (n=1)		
Polyuria	1	
Total treatment-related adverse events[a]	**32**	**8**

[a] Patients could report more than one adverse event at the same or different timepoints.

Table 2: Adverse events in which a causal relationship to THC:CBD oromucosal spray could not be ruled out by physicians.

	After 6 months' exposure (n=204)	After 12 months' exposure (n=143)
Patients who sought medical attention because of an injury caused by a fall	0	0
Patients with suicidal thoughts or suicide attempt	0	0
Patients having experienced other significant psychiatric or psychotic events Depressive syndrome Psychotropic effects Suspicion that it is related to THC:CBD spray?	4 3 (mild) 1 (moderate) 4	1 1 (mild) 0 1
Has the patient had any change in the ability to drive? Improvement No changes Loss Not applicable	 5 (2.5%) 71 (34.8%) 1 (0.5%) 127 (62.3%)	 2 (1.4%) 55 (38.5%) 0 86 (60.1%)
Has the patient had any other clinically relevant adverse event?	25 (12.3%)	11 (7.7%)

Table 3: Adverse events of special interest with cannabinoid-based medications.

resistance in the study population. Use of concomitant medications for MS, MS spasticity or other comorbid conditions remained stable in the majority of patients following introduction of add-on THC:CBD spray.

THC:CBD spray was generally well tolerated by patients during the first 12 months of use. The number of adverse events in which a causal relationship to THC:CBD spray could not be ruled out was low (n=40) and events were largely mild to moderate in severity. The lower incidence of adverse events (8 *vs* 32 events) in the second 6-month observation period may reflect development of tolerance to adverse events in patients with continued use and /or prior treatment discontinuations due to lack of tolerability. None of the 3 deaths that occurred was considered by the treating physician to be related to THC:CBD spray. The tolerability profile of THC:CBD spray in Spanish patients aligns with that reported in the observational MObility improVEment 2 (MOVE 2) study from Germany in which THC:CBD spray was prescribed to patients with treatment-resistant MS spasticity (n=300) according to approved labelling [19,20].

Although available clinical evidence suggests that THC:CBD spray is unlikely to be associated with 'cannabis-like' effects given the much lower THC blood levels compared with smoked cannabis [21-24], their occurrence cannot be ruled out entirely during wider and long-term use. As such, 'adverse events of special interest' were a primary focus of the safety evaluation. After 6 and 12 months' exposure, there were no incidences of suicidal ideation/attempts, a low incidence of psychiatric/psychotic events (4 mild events; 1 moderate event) and no indication of driving impairment. Two mild falls were recorded during the observation period but neither patient sought medical attention because of injury. It is worth noting that psychiatric symptoms and falls are known to be common in patients with MS irrespective of the presence of spasticity, and their risk increases in line with disease progression and degree of disability [25-27].

Although this was primarily a safety study, patient continuation rates provided a measure of effectiveness. After 6 and 12 months' exposure, respectively, treating physicians considered that 139 patients (68% of the original cohort) and 124 patients (60.5% of the original cohort) with moderate or severe MS spasticity who had not responded adequately to other antispasticity medications were deriving sufficient benefit from THC:CBD spray to warrant continued use.

Among patients who discontinued THC:CBD spray permanently during the observation period because of lack of efficacy and/or lack of tolerability, approximately half discontinued during the first 4-5 weeks of treatment which accords with the trial of therapy approach. On the basis of work by Farrar *et al.* [28], prescribing information for THC:CBD spray states that patients must show clinically noticeable improvement in spasticity-related symptoms (e.g. ≥ 20% improvement on the spasticity 0-10 Numerical Rating Scale) during an initial trial of therapy to continue with treatment [17]. As most people who benefit from THC:CBD spray do so within the first four weeks [15], limiting exposure to responders further enhances its safety in wider use.

These results complement the ECTRIMS 2013 congress reported interim analysis of the ongoing UK/Germany patient registry in which safety data were retrospectively reported for 687 of 2335 patients (29%) prescribed THC:CBD spray since marketing authorisation in June 2010. Because the population included many long-term users (i.e. patients treated continuously with THC:CBD spray since pre-authorisation compassionate use), median exposure was 570 days. At the time of analysis, 74% of patients were continuing with treatment and the median dose was 4.0 sprays/day. The most common adverse events reported were fall (34 patients; 4.9%), depression (23 patients; 3.3%), dizziness (13 patients; 1.9%), multiple sclerosis (13 patients; 1.9%) and urinary tract infection (10 patients; 1.5%). In addition, 9 patients each (1.3%) had multiple sclerosis relapse, fatigue, anxiety or nausea. Structured questioning on adverse events of special interest indicated that 6% of patients had reported a fall requiring medical attention, 1% reported suicidal thoughts and there was a single report of euthanasia. With respect to driving ability, 5% of patients reported improvement, 1% reported deterioration, 1% reported both, and 93% reported no change/not relevant/not reported.

Limitations of the current study include the relatively small sample size (n=205) for a post-marketing surveillance study; however, the report forms part of a wider commitment to health authorities to provide scheduled safety updates of THC:CBD spray in the first year immediately following marketing authorisation. The prospective nature of the study and loss of only a few patients to follow-up may compensate for the smaller sample size. It is also expected that prescribing clinicians will perceive value in receiving timely feedback about the safety of THC:CBD spray in patients who were prescribed THC:CBD spray for the first time. A degree of selection bias in the study population cannot be ruled out entirely as certain circumstances (e.g. perceived inability to complete questionnaires) allowed physicians to exclude patients from an invite to participate, although this is thought unlikely to have had any meaningful influence on the results. Measures implemented to minimise collection variation between centres and potential for patient recall bias included the use of standardised e-case report forms to record adverse events at each consultation and a scheduled review of patients' medical records after 6 and 12 months' exposure to THC:CBD spray to identify any adverse events reported at visits for reasons other than MS-related spasticity. Even so, there can be no guarantee as to the completeness and accuracy of the data captured by investigators.

Despite the limitations, this data analysis provides valuable information about the use of THC:CBD spray for MS-related spasticity in actual clinical practice settings in Spain. Although the focus of the analysis was primarily on safety, it is worth re-iterating that patients eligible for the study were treatment-resistant, i.e. they had spasticity not adequately controlled by existing antispasticity treatment. After 6 months' exposure to THC:CBD spray, 68% of this therapeutically-challenging group were considered by treating physicians to be deriving sufficient benefit to warrant continued treatment; the corresponding figure was 60.5% in patients with 12 months' exposure. As per approved conditions of use, THC:CBD spray was administered as add-on therapy to existing antispasticity medications and patients were able to self-titrate to optimal effect. The mean daily dosage (6.6 sprays/day) and low incidence of treatment-related adverse events after 6 and 12 months' exposure to THC:CBD spray indicates no misuse. Considered together, these findings suggest that patients with MS-related spasticity treated with THC:CBD spray are motivated to achieve sufficient benefit whilst limiting risk for adverse effects. Importantly, carer requirements did not change materially during the 12-month observation period despite the expected evolution in MS and MS spasticity over this timeframe.

Conclusions

This prospective, observational, multicentre study provides evidence of good safety and sustained benefit with use of THC:CBD spray in a relevant proportion of Spanish patients with treatment-resistant MS-related spasticity. After 6 and 12 months' exposure, add-on THC:CBD spray was not associated with any clinically-relevant occurrence of adverse events of special interest such as falls, psychiatric or psychotic symptoms, memory impairment, driving ability, or

addiction/abuse. The results are in line with interim analyses from a similar post-marketing study underway in the UK/Germany [16].

Acknowledgements

The authors would like to thank supporting staff in the clinical research organization for the conduction and statistical analyses of the project (GOC Networking, Barcelona Spain): Jessica Ruiz and Rosa Palomino; and also thank Kerry Dechant (Content Ed Net, Madrid, Spain) for editorial assistance with the manuscript, which was funded by Almirall S.A.

This study was sponsored by Almirall S.A., Barcelona, Spain.

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