



ORIGINAL ARTICLE

Clinical experiences with cannabinoids in spasticity management in multiple sclerosis^{☆,☆☆}

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Abstract

Introduction: Spasticity is a common symptom among patients with multiple sclerosis (MS).

This study aims to assess the effectiveness and safety of the combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in clinical practice for the treatment of spasticity in MS.

Methods: Retrospective observational study with patients treated with inhaled THC/CBD between April 2008 and March 2012. Descriptive patient and treatment variables were collected. Therapeutic response was evaluated based on the doctor's analysis and overall impression.

Results: Of the 56 patients who started treatment with THC/CBD, 6 were excluded because of missing data. We evaluated 50 patients (42% male) with a median age of 47.8 years (25.6–76.8); 38% were diagnosed with primary progressive MS, 44% with secondary progressive MS, and 18% with relapsing-remitting MS. The reason for prescribing the drug was spasticity (44%), pain (10%), or both (46%). Treatment was discontinued in 16 patients because of ineffectiveness (7 patients), withdrawal (4), and adverse effects (5). The median exposure time in patients whose treatment was discontinued was 30 days vs 174 days in those whose treatment continued at the end of the study. THC/CBD was effective in 80% of the patients at a median dose of 5 (2–10) inhalations/day. The adverse event profile consisted of dizziness (11 patients), somnolence (6), muscle weakness (7), oral discomfort (2), diarrhoea (3), dry mouth (2), blurred vision (2), agitation (1), nausea (1), and paranoid ideation (1).

Conclusions: THC/CBD appears to be a good alternative to standard treatment as it improves refractory spasticity in MS and has an acceptable toxicity profile.

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PALABRAS CLAVE

Cannabidiol;
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 Espasticidad

Experiencia clínica con los cannabinoides en la terapia de la espasticidad en la esclerosis múltiple

Resumen

Introducción: La espasticidad es un síntoma muy frecuente entre los pacientes con esclerosis múltiple (EM). El objetivo del presente estudio es evaluar la efectividad y la seguridad de la combinación de delta-9-tetrahidrocannabinol (THC) y cannabidiol (CBD) en la práctica clínica del tratamiento de la espasticidad en EM.

Métodos: Estudio observacional retrospectivo con los pacientes tratados con THC/CBD inhalado de abril del 2008 a marzo del 2012. Se recogieron variables descriptivas de paciente y tratamiento. La respuesta se evaluó mediante impresión global de respuesta terapéutica analizada por el médico.

Resultados: Cincuenta y seis pacientes iniciaron tratamiento, 6 fueron excluidos por falta de datos. Se evaluó a 50 pacientes (42% hombres), mediana de edad 47,8 años, el 38% de ellos diagnosticados de EM primaria progresiva, el 44% de EM secundaria progresiva y el 18% de EM remitente recurrente. El motivo de prescripción fue espasticidad (44%), dolor (10%) o ambos (46%). Se suspendió tratamiento en 16 pacientes por ineffectividad (7 pacientes), abandono (4) y efectos adversos (5). La mediana de tiempo de exposición de los pacientes que suspendieron tratamiento fue 30 días y 174 días para los que continuaban tratamiento al final del estudio. THC/CBD fue efectivo en un 80% de pacientes, con dosis mediana de 5 (2-10) pulverizaciones/día. El perfil de efectos adversos fue: mareo (11 pacientes), somnolencia (6), debilidad muscular (7), molestias bucales (2), diarrea (3), sequedad de boca (2), visión borrosa (2), agitación (1), náuseas (1), ideas paranoides (1).

Conclusiones: THC/CBD se muestra como una buena alternativa al tratamiento habitual mejorando la espasticidad refractaria en la EM con perfil de toxicidad aceptable.

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Introduction

Spasticity is a very frequent symptom in patients with multiple sclerosis (MS) and may appear at some point in up to 85% of all patients.¹ In Spain, results from the recently published 6E study show that in a population of 2029 MS patients, two-thirds experience spasticity. Symptoms range from moderate to very severe in 40% of the cases.² Spasticity often affects quality of life not only in patients, but also their family and caregivers to a great extent.³ Currently available drugs used to treat spasticity and associated symptoms (pain, rigidity, spasms, etc.) generally present limited effectiveness and are poorly tolerated.^{4,5} In fact, actual use of these treatments is quite low. In the 6E study, 57% of the patients with spasticity were not treated with any drugs.²

Activation of the endocannabinoid system has been shown to have therapeutic utility in motor disorders associated with MS, including spasticity. It has also shown utility as treatment for different forms of pain of neuropathic or inflammatory origin.^{6,7} Recent years have brought advances in the development of drugs extracted from *Cannabis sativa* or synthetic molecules with a similar effect. In 2010, Spanish drug authorities approved the marketing of a standard combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1-to-1 proportion. This drug, administered as an oral spray, is indicated as an additional treatment for symptoms of moderate to severe spasticity in MS patients that have not responded correctly to other antispasmodic drugs.⁸ THC/CBD is a drug listed for

hospital use only, meaning that it can only be dispensed by hospital pharmacy departments.

As described by Oreja-Guevara in her recent review,⁹ both clinical trials and longer-term extension studies have shown that THC/CBD is well-tolerated, safe, and effective for reducing spasticity refractory to other treatments. The purpose of this study is to evaluate the effectiveness and safety profile of the THC/CBD combination in clinical practice as treatment for refractory spasticity in MS.

Patients and methods

This retrospective observational study evaluated all patients diagnosed with MS and treated with THC/CBD in our hospital from the first time the treatment was used in April 2008 up to March 2012. All patients with refractory spasticity who began treatment with vaporised THC/CBD (Sativex® oral spray, 2.7 mg THC/2.5 mg CBD) attended at least one session with the nurse educator at the MS unit. Dosing and any side effects were monitored by monthly telephone calls. The drug was dispensed monthly by the pharmacy unit for outpatients at the hospital pharmacy department. Study variables were sex, age, diagnosis, reason for prescription, concomitant medications, exposure time to THC/CBD, response, effective dose, and adverse effects. A dichotomous (yes/no) answer was given for 'response' based on the prescribing doctor's analysis and the overall impression of the patient's response to treatment. A univariate analysis was also performed to study the relationship

between treatment response and the variables sex, age, type of MS, concomitant medication, the appearance of adverse effects, dose, and duration of exposure to THC/CBD. We used the same analysis to study the relationship between the variables listed above and appearance of adverse effects.

Data were obtained by reviewing the patients' electronic medical histories (Orion Clinic[®]) and the computer application used by the pharmacy unit for outpatients. The Mann-Whitney test was used for categorical variables and Fisher's exact test for continuous variables. Statistical analysis was performed using SPSS[®] version 18.0.

Results

During the study period, 56 patients with MS began treatment with THC/CBD; 6 were excluded due to lack of data about effectiveness that would let us evaluate treatment response. The 50 evaluable patients (42% men) had a median age of 47.8 years (25.6-76.8). The patient population consisted of 38% diagnosed with primary progressive MS, 44% with secondary progressive MS, and 18% with recurring remitting MS. The reasons for prescribing THC/CBD were spasticity (44%), pain (10%), or both (46%), that were refractory to the usual treatments. Antispasmodic drugs were concomitantly taken by 52% of the patients with a mean of 2 drugs per patient. Drug distribution was as follows: baclofen 20 patients, tizanidine 7, diazepam 5, gabapentin 4, carbamazepine 3, clonazepam 2, amitriptyline 1, pregabalin 1, oxcarbazepine 1, and botulinum toxin 1. During the study period, THC/CBD treatment was suspended in 16 patients due to lack of effect ($n=7$), non-compliance ($n=4$), and adverse effects ($n=5$). Median drug exposure time among patients whose treatment was suspended was 30 days (5-263); median exposure time was 174 days (23-1422) among those who were still being treated at the end of the study.

Treatment was effective in 80% of the patients, with a median optimum maintenance dose of 5 (2-10) sprays per day.

One or more adverse effects were presented in 52% of the patients in the following order of frequency: dizziness ($n=11$), muscle weakness ($n=7$), somnolence ($n=6$), diarrhoea ($n=3$), oral discomfort ($n=2$), dry mouth ($n=2$), blurred vision ($n=2$), agitation ($n=1$), nausea ($n=1$), and paranoid ideation ($n=1$). Adverse effects were mild in the 5 patients in whom treatment was suspended and mainly consisted of weakness, dizziness, and oral discomfort.

There were no statistically significant differences related to treatment response and sex ($P=.488$), age ($P=.574$), type of MS ($P=.933$), concomitant use of antispasmodic drugs ($P=.570$), appearance of adverse effects ($P=.251$), and daily dose of THC/CBD ($P=.251$). Likewise, we found no statistically significant differences between appearance of adverse effects and sex ($P=.633$), age ($P=.806$), type of MS ($P=.571$), concomitant antispasmodic drugs ($P=.598$), dose ($P=.416$), and drug exposure time to THC/CBD ($P=.844$).

Discussion

This study was designed to evaluate THC/CBD effectiveness and safety in clinical practice as a symptomatic treatment for refractory spasticity in patients diagnosed with MS. Regarding our first objective, we can state that THC/CBD was highly effective (80%) in our series of 50 cases. This finding is similar to that described in the clinical trial by Novotna et al.¹⁰ in which 74% of the patients responded to treatment, keeping in mind that this group of study patients were considered 'responsive' if they experienced at least a 30% decrease in spasticity compared to the baseline reading, measured on the Numeric Rating Scale (NRS). None of the variables analysed in this study sample was identified as having a statistically significant impact on treatment response. It is true that the method used to measure response (prescribing doctor's overall impression of treatment response) could reflect the influence of subjective factors associated with either the doctor or the patient. Clinical trials and extension studies have used the NRS¹¹ and/or the Ashworth scale.¹² However, the NRS itself is not free from subjective factors given that it is filled in by patients themselves. On the other hand, a recent study shows that the Ashworth scale is not a good means of evaluating spasticity.¹³ Since this is a retrospective study, the data it contains are those taken from daily clinical practice, a situation in which use of more complex scales would result in significant data loss. The higher effectiveness of the treatment in our case series compared to that described in clinical trials may be due to the work of the educator nurse who checks doses and detects adverse effects throughout the duration of treatment. This may result in better treatment compliance and adherence, leading in turn to increased effectiveness.

On the other hand, the fact that mean drug exposure time in patients whose treatment was suspended was 30 days coincides with the recommendation in the summary of product characteristics that treatment is to be discontinued after 4 weeks in patients with refractory disease.⁸ Use of this initial trial period optimises the benefits of the drug since it allows us to identify patients for whom a favourable response, without side effects, may be expected.

The optimum maintenance dose for the patients in our study, 5 sprays/day, was lower than that described by Notcutt et al.¹⁴ (8.25 sprays/day) or by Novotna et al.¹⁰ (8.3 sprays/day). None of our patients exceeded 12 sprays/day, which is in line with instructions in the summary of product characteristics.⁸ On this subject, we must stress that since the study was retrospective, we could not control concomitant use of antispasmodics. This situation may be a confounder given that it did not remain stable throughout the study. In any case, 48% of the patients did not take additional antispasmodic drugs, and this percentage is lower than that described in the 6E study (57%).

Regarding safety, our 52% incidence of adverse events was lower than the rate of 84% found in a meta-analysis of all patients from 5 controlled and randomised clinical trials.¹⁵ However, it is similar to the 53% rate present in the clinical trial by Novotna et al.¹⁰ This is because that trial and our study both employed gradual up-titration, and this practice is associated with lower rates of adverse effects compared to those found in other clinical trials. These studies also showed similar profiles for adverse events; effects

were typically dose-dependent, and they included mild or moderate dizziness in the first few weeks of treatment that could be managed by adjusting the dose correctly. None of the patients in whom treatment was suspended due to poor tolerance presented severe adverse effects. The typical psychotropic effects associated with consumption of cannabis as a recreational drug appeared only infrequently, as was also the case in the clinical trials. Furthermore, our series did not contain any cases at risk for drug tolerance, abuse, or addiction.

None of the study variables was identified as having a statistically significant effect on the appearance of adverse effects.

While mindful of the limitations intrinsic to a small and heterogeneous case series, we would point out that the study has the advantage of presenting daily clinical practice outside the highly controlled context of clinical trials. In conclusion, the THC/CBD combination proved itself a good alternative to usual treatments in our study, and it improved symptoms of refractory spasticity in MS patients with an acceptable toxicity profile. Prospective studies are needed to confirm our results and help identify response and safety markers for treatment with THC/CBD.

Conflict of interest

The authors have no conflicts of interest to declare.

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