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Title: PRELIMINARY RESULTS USING CANNABIS BASED MEDICINAL EXTRACT FOR REFRACTORY LOWER URINARY TRACT DYSFUNCTION IN PATIENTS WITH ADVANCED MULTIPLE SCLEROSIS

Aims of Study

Indwelling catheterisation may be the only therapeutic option for patients with advanced multiple sclerosis (MS; Kurtzke $\geq$ 6.5) and troublesome bladder symptoms secondary to detrusor hyperreflexia (DH) and detrusor-sphincter dyssynergia (DSD). Favourable anecdotal reports on the effects of cannabis on bladder symptoms in MS together with basic research studies in animals demonstrating the existence of cannabinoid receptors in both the bladder and brain regions associated with bladder control encouraged further clinical investigation of cannabinoids as a possible alternate therapeutic option for these patients. Therefore, when cannabis-based medical extract (CBME) became available for clinical trials, this open-label pilot study was initiated. Its primary aim is to evaluate the safety, tolerability and efficacy of a preparation of sub-lingual CBME in patients with advanced MS and refractory lower urinary tract symptoms (LUTS) in whom indwelling catheterisation is being considered.

Methods

To date (March, 2001), 13 patients from an anticipated total of 24 with advanced MS and refractory LUTS secondary to DH have been recruited into the study, and 11 are on treatment. Inclusion criteria include DH demonstrated by cystometry and troublesome LUTS (identified by a frequency-volume-incontinence [FVI] chart and the ICS- BPH and BFLUTS urinary symptom questionnaires). Exclusion criteria include an indwelling catheter and mini-mental state examination score <27. Following the screening visit to assess suitability for the study, there is a run-in period during which baseline symptoms are formally recorded using FVI charts and pad testing where applicable for 3 days per week for three- weeks. At the dosing visit, the patient is instructed on the use of the sublingual spray device. Each spray contains equal amounts delta-9-tetrahydrocannibinol (THC, 2.5mgs) and cannabidiol (CBD, 2.5mgs). Under supervision in the department, the patients take up to a total of 4 sprays if tolerated, equivalent to 10mgs of THC and 10mgs of CBD.

Patients begin by taking this preparation of the CBME only at night for the first 2 weeks, gradually increasing the dose until urinary symptom relief has been achieved or unacceptable side effects occur. After 2 weeks, daytime dosing is gradually introduced, with the patient increasing the number of sprays as necessary. The patients complete FVI charts and pad tests for 3 days per week, every week to identify cumulative, dose-related effects. Drug consumption and side effects are recorded daily and are also monitored by regular telephone contact.

To assess the acute effects of CBME on lower urinary tract function, cystometry is performed (with serum cannabinoid levels) before and after maximum tolerated dose of CBME at 4, 8 and 16 weeks on treatment.

Results

To date, one of the 13 patients patient was withdrawn due to a possible adverse reaction to the drug, whilst another was withdrawn due to a relapse of her MS, and 4 are in the initial stages of the study. Here we report results of 7 patients (1M:6F, age range 31-51) followed completely through to the 4th clinic visit (8 weeks after beginning use of CBME).

All 7 patients showed improvement in some aspect of their urinary symptoms. The mean number of episodes of incontinence for the first seven evaluable patients decreased from 2.8 at baseline to 1.2 after 8 weeks of treatment on CBME (Fig. 1), although this was not statistically significant (p= 0.06, paired t-test). The mean daytime frequency decreased from a mean of 10.1 to 8.0 (p=0.03, paired t-test). The mean maximum cystometric capacity (MCC) at 8 weeks without CBME use for the previous 24 hrs increased from a baseline of 302mls to 345mls (p=0.37, paired t-test), suggesting that there is no long-term effect. However, after administration of the maximum tolerated dose of CBME at the 8 week visit (dose range 5mg CBD & 5mg THC-40mg CBD & 40mg THC) the MCC increased to 439mls (p=0.04, paired t-test), suggesting an acute effect (Fig. 2).

Conclusions

These preliminary pilot results indicate that CBME may prove to be an effective additional treatment for ameliorating some urinary symptoms in a selected group of patients with advanced multiple sclerosis.

Figure 1.

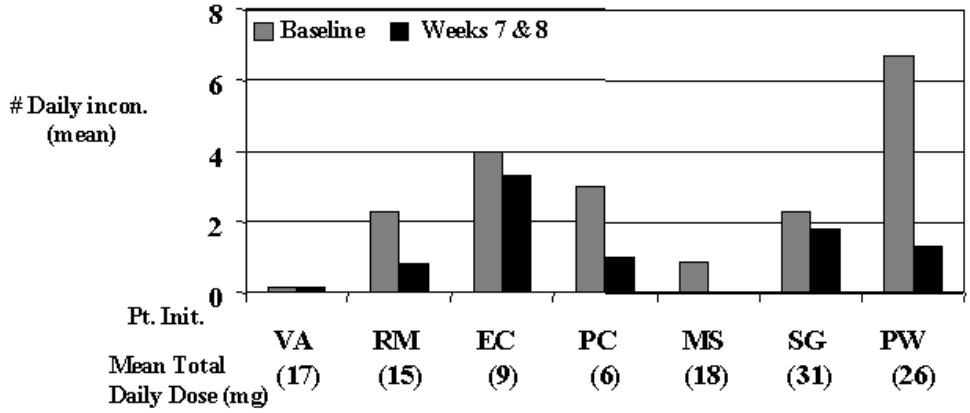

Figure 2.