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ORIGINAL COMMUNICATION

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Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain

A double-blind placebo-controlled cross-over trial

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Abstract About 30% of patients with chronic upper motor neuron syndrome (UMNS) suffer from disabling spasticity-related pain not sufficiently correctable by conventional treatment. Delta9-tetrahydrocannabinol (Δ^9-THC) was reported to add benefit in the treatment of pain in patients with multiple sclerosis (MS). The question arose whether synthetic cannabinoids with lower potential for psychotropic side effects could be effective as well. To evaluate the safety and efficacy of low dose treatment with the synthetic cannabinoid Nabilone (1 mg per day) on spasticity-related pain a placebo-controlled double-blind crossover trial was performed.

11 out of 13 included patients completed the study. The 11-Point-Box-Test showed a significant decrease of pain under Nabilone ($p < 0.05$), while spasticity, motor function and activities of daily living did not change.
5 patients reported side effects: one moderate transient weakness of the lower limbs (Nabilone phase, drop out), three mild drowsiness (two Nabilone, one placebo) and one mild dysphagia (placebo). One patient was excluded from the study due to an acute relapse of multiple sclerosis (Nabilone phase, drop out).

Nabilone 1 mg per day proved to be a safe and easily applicable option in the care of patients with chronic UMNS and spasticity-related pain otherwise not controllable.

Key words Nabilone · synthetic cannabinoid · spasticity · central pain

Introduction

About 30% of patients with chronic UMNS suffer from spasticity-associated pain. About half of these patients do not respond to conventional analgesic management and therefore effective treatment is missing [1]. A recent review of antispastic treatment options in multiple sclerosis (MS) suggested that cannabinoids might be a valuable and cost effective addition to standard treatment [2]. Systemically administered Δ^9-THC has anti-nociceptive and anti-hyperalgesic effects [3], and spasticity could be reduced by endocannabinoids in different animal models [4].

The question arises whether synthetic cannabinoids are effective in spasticity-related pain management in patients with UMNS. This is of particular interest in the context of lower potential for side effects in synthetic cannabinoids. Nabilone is a benzopyrane derivate synthetic cannabinoid. It is

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active when taken orally, lipid-soluble and crosses blood-brain barrier quickly. The bioavailability is 95.8%. Elimination half life averages 2 hours, degradation passes several active hydroxyl-metabolites with half life up to 36 hours. It binds to cannabinoid receptors like Δ^9-THC but was found to be without psychoactive properties [5, 6]. It is the only legally available cannabinoid preparation in the United Kingdom and is licensed solely for use in reduction of nausea and vomiting induced by chemotherapy [7, 8].

To evaluate tolerability and efficacy of low dose treatment with Nabilone on spasticity-related pain syndromes refractory to conventional treatment a placebo-controlled double-blind crossover trial was initiated. The study also assessed neuropsychological items relevant for driving ability in a subset of patients [9].

Patients and methods

13 patients (for details see table 1) with chronic upper motor neuron syndrome (UMNS) were included in the study. For inclusion they had to suffer from disabling spasticity-related pain refractory to previous pain treatment (table 1). Spasticity-associated pain was defined as pain sensation corresponding to increased spastic muscle tone while passively moving the painful body segment or limb [10]. To differentiate from other forms of pain passive stretch of the involved spastic muscles had to result in increase of pain perception in the stimulated muscles or related joint region. Painful muscle spasms alone were not sufficient for inclusion in the study.

6 patients participated in an extended study regarding cognitive performance which has been reported elsewhere [9].

The study was performed as a double-blind, randomised, placebo-controlled crossover study with a total duration of 9 weeks. Pre-medication and physical therapy remained unchanged during the study period. Nabilone or matching placebo (supplied by AOP Orphan, Great Britain) were given over a period of 4 weeks as capsules of identical colour and taste (first week 0.5 mg Nabilone per day, three weeks 1 mg Nabilone per day or matching placebo capsule). This dose was chosen after an open pilot trial with three patiens suffering from spasticity related pain (not included in the present study), who responded favourably to 1 mg Nabilone. Patients were randomly assigned to receive either Nabilone or placebo first. Following a one week "wash-out"-phase patients on placebo were switched to Nabilone and vice versa (figure 1). Probands were not allowed to use any other cannabis-based medication during the study.

Evaluation included 11-Point-Box-Test (pain rating)as the primary and Ashworth-Score (spasticity rating), Rivermead-Motor-Assessment (motor performance test), and Barthel-Index (activities of daily living) as secondary outcome measures at baseline, end of treatment-phase1, end of wash-out, and at the end of treatment-phase2. Use of different medication and side effects were recorded. Data were analysed by descriptive statistics and by analysis of variance (ANOVA) considering the factors subject, medication (Nabilone, placebo) and treatment period.

The local Research Ethics Committee approved the study and all patients gave written informed consent to the study and the neuropsychological testing.

Results

Eleven out of 13 patients completed the trial. Two drop-outs occurred in patients with MS due to acute relapse (n = 1, two days after start of Nabilone treatment) and exacerbation of weakness in the lower limbs (n = 1, 14 days after start of Nabilone). No other severe side effects were reported (table 2).

The 11-Point-Box-Test as a measure of spasticity-related pain decreased for a median 2 points with Nabilone compared with placebo treatment ($p < 0.05$). Placebo treatment showed no change in 11-Point-Box-Test ($p = 0.8$). Intensity of pain as rated by 11-Point-Box-Test was the same at baseline and after one week of wash out (median 6.0, $p = 0.6$). This showed that the interval between the two treatment arms was adequate (figure 2).

Spasticity as assessed by Ashworth scale was reduced from mean 1.7 (SD 1.224)(baseline) to mean 1.347 (SD 1.234)(placebo) or mean 1.0 (SD 1.291)(Nabilone) ($p = 0.4$). Dexterity (Rivermead Motor Assessment) and functional integrity in activities of daily life (Barthel-Index) showed no change with either Nabilone or placebo.

Discussion

A recent metaanalysis of 9 randomised controlled studies assessed analgesic efficacy of cannabinoids (Δ^9-THC and synthetic analogues) in 222 patients with cancer, chronic non-malignant, and postoperative pain. Results for acute and cancer pain were quite disappointing, while neuropathic pain responded better (referring to the study of Maurer et al. [11] with only one patient).

This first controlled study of Nabilone (1 mg/d) in patients with spasticity associated pain showed significant analgesic efficacy. Two single case studies earlier had indicated that this synthetic cannabinoid could reduce neuropathic pain [12, 13].

The present study paralleled the findings of the recently published multicentre randomised placebo-controlled trial in the UK on Δ^9-THC in chronic MS [14]. Patients in this study felt that pain was significantly reduced under Δ^9-THC or cannabis extract in comparison with placebo. The authors speculated that cannabinoids might have a more specific role in the management of chronic neuropathic pain than other analgesic substance classes.

On the other hand, ratings on the Ashworth scale, Rivermead assessment and Barthel index remained unchanged between baseline and the end of the medication phase indicating no considerable improvement in spastic muscle tone, motor function

Table 1 Patient details

Case	Diagnosis / date of dg.	Age(years)	Sex	Current main problem	Previous therapies	Current medication
WH	Secondary progressive multiple sclerosis / 2000	63	f	Spastic tetraplegia	Tetrazepam 50 mg 1x, Baclofen 10 mg 2x1, Tramadol 20 gtt	Gabapenin 4x400 mg, Tizanidin 3x4 mg, Baclofen 3x25 mg
GT	Secondary progressive multiple sclerosis / 2001	19	f	Spastic tetraplegia	Tetrazepam 50 mg 1x, Baclofen max 30 mg/d	Naproxen 2x500 mg, Tetrazepam 2x50 mg
FS	Secondary progressive multiple sclerosis / 1998	42	f	Spastic paraplegia	Baclofen 25 mg2x1, Tizanidin 8 mg/d	Baclofen 20 mg/d, Tizanidin 8 mg/d, Botulinumtoxin A (Dysport®) 1000 MU
KM	Secondary progressive multiple sclerosis / 1993	52	f	Spastic paraplegia	Baclofen 50 mg/d	Gabapentin 1800 mg/d
GE	Relapsig remitting multiple sclerosis / 1984	54	f	Spastic tetraplegia	Carbamezepin ret. 300 mg, Amitriptylin 75 mg ret., Tizanidin 4 mg/	Tizanidin 6 mg/d
SR	Secondary progressive multiple sclerosis / 1988	38	f	Spastic paraplegia	Baclofen 25 mg 4x1 Tizanidin 3 x2 mg	Gabapentin 3x300 mg, Baclofen 100 mg, Tizanidin 6 mg
BM	Secondary progressive multiple sclerosis / 1999	34	f	Spastic paraplegia	Baclofen 75 mg/d, Tramadol gtt 3 x20	Gabapentin 3 x400 mg, Baclofen 100 mg/d
VR	Traumatic spinal injury / 1997	45	m	Spastic tetraplegia	Tizanidin 4 x2 mg, Baclofen 10–10–10–25 mg, Gabapentin 3x400 mg	Tizanidin 4x2 mg, Baclofen 10–10–10–25 mg, Gabapentin 3x400 mg
BG	Left hemisphaeric ischaemic infarction cardioembolic/1998	68	m	Rightsided Spastic Hemiparesis	-	Botulinumtoxin A (Dysport®) 650 MU, Buprenorphin TTS (35)
PH	Traumatic spinal injury / 1992	42	m	Spastic paraplegia	Botulinumtoxin A (Botox®) 400 MU	Botulinumtoxin A (Botox®) 270 MU
BB	Traumatic cerebral injury / 1987	34	f	Leftsided Spastic Hemiparesis	Baclofen 75 mg/d, Botulinumtoxin A (Dyspprt®) 1000 MU,	Baclofen 75 mg
SJ	Traumatic spinal injury / 1999	30	m	Spastic paraplegia	Baclofen intrathecal	Baclofen intrathecal
MJ	Intracerebral hemorrhage / 1998	62	f	Leftsided Spastic Hemiparesis	Botulinumtoxin A (Dysport®) 1000 MU, Baclofen 50 mg/d, Carbamazepin 300 mg, Paracetamol 500 mg	Baclofen 50 mg/d, Carbamezepin 300 mg, Paracetamol 500 mg

and ADL, as also reported by Zajicek et al. [14]. In the literature, the antispastic efficacy of cannabinoids is considered controversial. Petro et al. used a single dose application of Δ^9-THC and found significant reduction of spasticity in MS patients with minimal side effects [15], Meinck saw the same effect in a MS patient smoking a cannabis cigarette [16]. Maurer et al. in a single case double blind study reported marked reduction of spasticity with Δ^9-THC in a man with spastic paraplegia following spinal ependymoma [11]. Also Brenneisen et al. saw improvement of spasticity, walking ability and pain in two patients under open label Δ^9-THC without psychotropic side effects [17]. Objective neurological ratings were unchanged but patients felt subjectively less spastic after oral Δ^9-THC [18] or after smoking cannabis [19]. On the other hand Kogel et al. and Killestein et al. observed worsening of spasticity and cognitive as well as emotional side effects with dronabinol or cannabis plant extract [20, 21]. Killestein et al. reviewed the literature and still found no convincing evidence of spastic reducing properties of cannabinoids in humans [22]. Despite this conclusion and sometimes serious legal problems [23], numerous patients with e.g. multiple sclerosis demand cannabinoids for relieving spasticty following their subjective positive experiences [24].

The mechanism of cannabinoid action in spasticity-related pain in humans is not known. Spinal CB1 receptors enhance GABA neurotransmission and seem to modulate pain thresholds tonically [25], but endogenous cannabinoids and cannabinoid receptors exist from peripheral sensory nerve endings to spinal cord and supraspinal centres in the pain pathways [3, 26, 27]. The discrepancy of the antispastic effects in experimental animals and humans is not readily explained. It has been speculated that the assessment methods in human studies, especially the Ashworth Scale, were too insensitive for subtle treatment effects observed by the patients themselves [26].

During the present study low dose treatment of Nabilone was well tolerated. The relapse of MS leading to withdrawal of one patient could not be related to the pharmacodynamic properties of the substance. Cannabinoids are regarded as anti-inflammatory and neuroprotective in MS alleviating the progression of

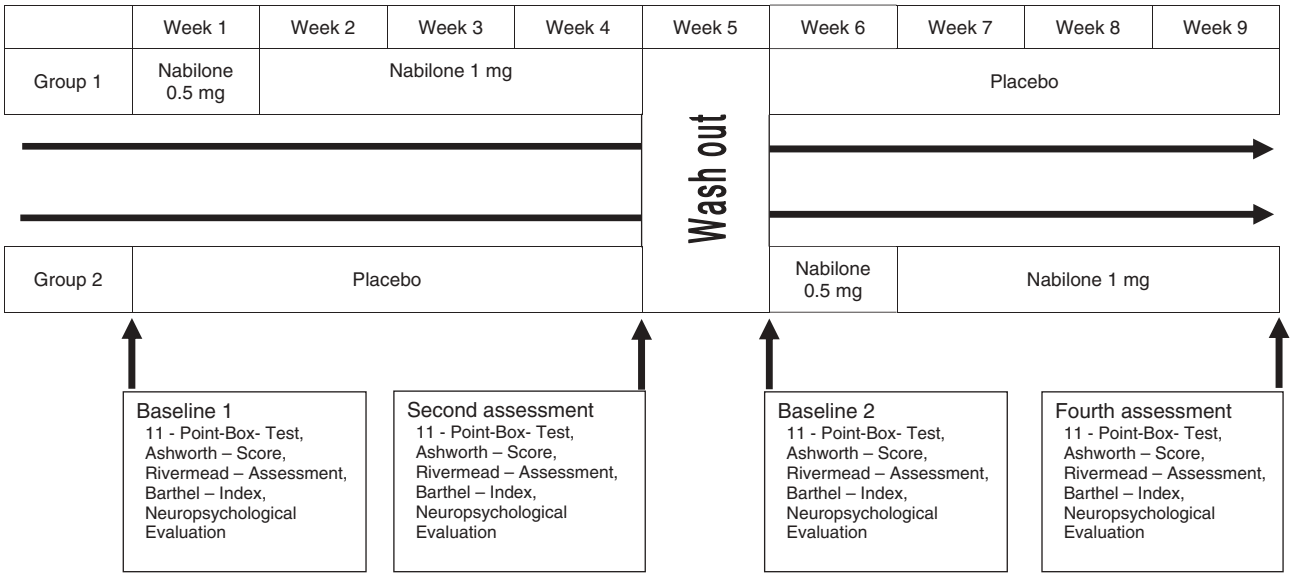

Fig. 1 Study procedure

Table 2 Side effects

	Nabilone	Placebo
severe (drop out)		
relapse of MS	1	0
weakness of lower limbs	1	0
not severe		
drowsiness	2	1
dysphagia (slight)	0	1
weakness in the lower limbs (slight)	1	0

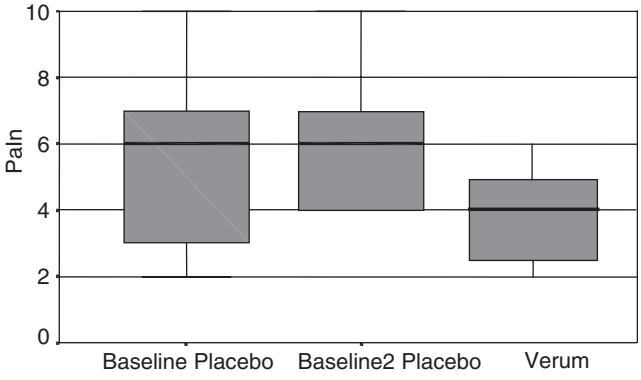

Fig. 2 11-Point-Box-Test at baseline 1 and 2 and with Nabilone treatment

disease, although detailed human studies are missing [28]. In their sample of 404 Cannabinoid-treated MS patients Zajicek et al. reported no increase in relapses compared with placebo [14].

One patient dropped out because of weakness of lower limbs which could be attributed to Nabilone effect. Although Ward et al. stated that "The incidence of side effects is high with Nabilone, drowsiness, dizziness and/or vertigo occur in 60 to 70% of patients" [8], the other side effects observed in the present study were stated as mild and easily tolerable. A parallel study of neuropsychological performance in a sub-sample of the total cohort showed no cognitive side effects in domains of attentional performance, psychomotor speed, and mental flexibility [9].

It may be that the limited relative efficacy and adverse effect profile in comparison with opiate drugs argue against widespread use of cannabinoids in clinical practice [29, 30]. However, central and peripheral neuropathic pain and spasticity-related pain often present a challenge to therapeutic options. In selected patient groups with otherwise uncontrollable spasticity-related pain, Nabilone proved to be a worthwhile and safe addition to the therapeutic armamentarium. The ease of application, the benefit greater than standard treatment, and the good tolerability of Nabilone should lead to studies in management of spasticity related pain with larger a sample size. Nabilone seems a useful amendment in the treatment of such pain syndromes.

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