Treatment of Tourette-Syndrome with Δ^9-Tetrahydrocannabinol (THC): a randomized crossover trial

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Summary

Anecdotal reports in Tourette-Syndrome (TS) suggested that marijuana (cannabis sativa) and delta-9-Tetrahydrocannabinol (Δ^9-THC), the major psychoactive ingredient of marijuana, reduce tics and associated behavioral disorders.

We performed a randomized double-blind placebo-controlled crossover single-dose trial of Δ^9-THC (5.0, 7.5 or 10.0 mg) in 12 adult TS patients. Tic severity was assessed using a self rating scale (Tourette Syndrome Symptom List, TSSL) and examiner ratings (Shapiro Tourette-Syndrome Severity Scale, Yale Global Tic Severity Scale, Tourette-Syndrome Global Scale). Using the TSSL, in addition, patients rated the severity of associated behavioral disorders. Clinical changes were correlated to maximum plasma levels of THC and its metabolites 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic-acid (THC-COOH).

Using the TSSL there was a significant improvement of tics ($p = 0.015$) and obsessive compulsive behavior (OCB) ($p = 0.041$) after treatment with Δ^9-THC compared with placebo. Examiner ratings demonstrated a significant difference for the subscore “complex motor tics” ($p = 0.015$) and a trend towards a significant improvement for the subscores “motor tics” ($p = 0.065$), “simple motor tics” ($p = 0.093$), and “vocal tics” ($p = 0.093$). No serious adverse reactions occurred. Five patients experienced transient mild side effects. There was a significant correlation between tic improvement and maximum plasma concentration of 11-OH-THC.

Results obtained from this pilot study suggest that a single-dose treatment with Δ^9-THC is effective and safe in the therapy of tics and OCB in TS. It can be speculated that clinical effects may be caused by 11-OH-THC. A longer term study is needed to confirm these data.

Introduction

Gilles de la Tourette-Syndrome (Tourette-Syndrome, TS) is a complex neurobehavioral disorder characterized by multiple motor tics and one or more vocal tics throughout a period of more than a year, onset before age 18. Basal ganglia circuits projecting to frontal and limbic areas and the dopaminergic system seem to be pathophysiologically involved. Presently, dopamine antagonists are the most effective drugs for the treatment of tics (18, 22).

Anecdotal reports (5, 24) and a retrospective survey using a standardized interview (19) suggested a beneficial influence of marijuana smoking on tics and associated behavioral disorders in TS. Therefore, in an open uncontrolled pilot study we have treated one patient once with 10 mg delta-9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive ingredient of marijuana. Using the Tourette's Syndrome Global Scale (12) the total tic severity score was 41 before treatment and was reduced to 7 two hours after treatment. The patient noted a tic improvement of 70% and felt an amelioration in attention, impulse control, obsessive-compulsive behavior (OCB), and premonitory feeling without having any adverse reactions (20).

This pilot study was carried out to confirm these preliminary results suggesting that Δ^9-THC might be successful in the therapy of TS. Therefore, we performed a randomized double-blind placebo-controlled crossover trial of Δ^9-THC in 12 adult patients suffering from TS.

Method

Patients

In this study 12 adult patients (11 men, 1 woman, mean age = 34 ± 13 (SD) years, range, 18 – 66 years) with TS according to DSM-III R criteria were included. Patients were recruited from our movement disorder clinic. Tic severity was measured according to the Shapiro Tourette-Syndrome Severity Scale (STSS) (26), the Tourette-Syndrome Global Scale (TSGS) (12), and the Yale Global Tic Severity Scale (YGTSS) (3) by one of the authors who is very experienced in Tourette-Syndrome and tic rating (KR MV). Before entering the study tic severity (mean (±SD) / median) was 3.6 (±1.2) / 4 (STSS), 22.6 (±22.0) / 22 (TSGS), and 45.8 (±17.3) / 46 (YGTSS). Seven patients were unmedicated for at least two years and five were taking medication for the treatment of TS (two patients pimozide (no. 1 and 4), one tiapride (no. 11), one diazepam (no. 3), and one pimozide, clonazepam and fluoxetine (no. 9)). Medication was stable for at least two months before entering the study and during the course of the study. Patients were excluded who had significant concomitant illnesses, history of psychosis and schizophrenia, and pregnancy. In all patients routine blood and urine tests and MRI were done to exclude other diseases.

Seven patients reported prior use of marijuana: three (no. 2, 7, 10) had used marijuana only once or occasionally years ago and four (no. 1, 5, 8, 12) were regular users but were asked to stop using marijuana at least one week before entering the study. Five patients (no. 3, 4, 6, 9, 11) had never used marijuana before.

The study was approved by the local ethic committee, the German Federal Institute for Drugs and Medical Devices (Federal Opium Agency), and the district authority. For all patients an insurance was taken out. After complete description of the study to the subjects, written informed consent was obtained.

Design

The study was conducted as a double-blind placebo-controlled crossover trial. Patients were randomly assigned a single-dose of oral Δ^9-THC (gelatin capsules à 2.5 and 5.0 mg) first or a single-dose of identical placebo first on two days separated by a 4-week washout phase before they were crossed over to receive the other treatment. Randomization was done by a psychiatrist who was not involved in the study and kept the codes until completion of the study. None of the investigators or patients had access to the randomization codes during the study.

Patients received different doses of Δ^9-THC according to their body weight, sex, age and prior use of marijuana: females without prior use of marijuana and body weight $\leq$ 60 kg or age $\geq$ 50 years received 5.0 mg, otherwise 7.5 mg; men without prior use of marijuana and body weight $\leq$ 70 kg or age $\geq$ 50 years received 5.0 mg; men who used marijuana regularly, body weight > 70 kg and age < 50 years received 10 mg, all other men received 7.5 mg. Thus, four patients received 5.0 mg Δ^9-THC (no. 4, 6, 7, 10), six 7.5 mg (no. 2, 3, 5, 9, 11, 12) and two 10.0 mg (no. 1, 8).

On both days the same experimental plan was applied. Before medication patients got a standardized breakfast to guarantee comparable enteral absorption of Δ^9-THC. At baseline and hourly until 5 hours after medication blood pressure and pulse were taken. To measure plasma concentrations of THC and its metabolites 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic-acid (THC-COOH) blood samples were taken before and 30, 90, 150, 240, 360 and 1440 min (=24 hours) after medication. Patients remained in hospital for one night.

Each patient rated tic severity on a self rating scale according to the Tourette Syndrome Symptom List (TSSL) (12) before and 3-4 hours after treatment.

Furthermore, during an interview session tic severity was assessed before and 3-4 hours after treatment using different examiner ratings (STSS, YGTSS, and TSGS) by one of the authors (KR MV). Patients were unaware of tic rating. We analyzed not only total tic scores but also - dependent on the particular scale - subscores for the categories simple motor tics (SMT), complex motor tics (CMT), motor tics (MT = SMT + CMT), simple vocal tics (SVT), complex vocal tics (CVT), and vocal tics (VT = SVT + CVT). Using the TSSL, additionally, patients were asked to rate severity of impulse control, OCB, anxiety, depression, attention deficit hyperactivity disorder (ADHD), and premonitory experiences (PE) prior to the occurrence of tics before and after treatment (0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe). The symptom “OCB” was subdivided into obsessions and compulsions like checking, ordering, doing things just right, counting, rituals, washing, and doing things an exact number of times.

At the end of each examination day patients were asked to rate the global change (0, ±10%, ±20% etc. – ±100%) and document adverse reactions. At the end of the second day, in addition, they were asked which examination day they assessed overall as more positive (including global change and side effects; 0, 10%, 20% etc. – 100%).

The primary outcome measures were: tic scores according to the TSSL, STSS, YGTSS, and TSGS, scores of associated behavioral disorders measured by the TSSL, global change and plasma concentrations of THC, 11-OH-THC and THC-COOH.

Statistical analysis

To analyze results of self and examiner ratings differences were calculated between rating scores obtained before and after treatment either with Δ^9-THC or placebo. For all ratings treatment- , carry-over- and phase-effect were calculated using the method described by Hill and Armitage (7). The significance of differences in self and examiner ratings after treatment with Δ^9-THC compared with placebo was assessed using the Mann-Whitney test. Differences were considered significant if the probability of error was $p < 0.05$ and, in addition, carry-over- and phase-effect were not significant. Correlations between changes in clinical rating scores and maximum plasma concentrations of THC, 11-OH-THC, and THC-COOH were tested by simple linear regression analysis. A value of $p < 0.05$ was used to determine statistical significance. All tests were used in an exploratory manner. No correction for multiplicity of testing was done. Data were analyzed using SPSS PC version 7.0 for Windows.

Results

Six patients received Δ^9-THC then placebo and another six patients placebo then Δ^9-THC. None of the patients dropped out.

Using the TSSL there was a significant improvement of tics after treatment with Δ^9-THC compared with placebo ($p = 0.015$). Analyzing subscores of the TSSL there was a significant improvement of SMT ($p = 0.026$), CMT ($p = 0.015$), MT ($p = 0.026$), and CVT ($p = 0.041$) (table 1).

Using examiner ratings global tic severity scores demonstrated a much greater reduction after Δ^9-THC treatment compared with placebo but differences did not reach statistical significance (table 1). However, when analyzing subscores CMT (TSGS) demonstrated a significant improvement ($p = 0.015$) and there was a trend towards a significant difference for the subscores MT (TSGS, $p = 0.065$), SVT (TSGS, $p = 0.093$), and VT (TSGS, $p = 0.093$; YGTSS, $p = 0.093$).

Using the TSSL, in addition, there was a significant improvement of OCB ($p = 0.041$). Other categories of behavioral disorders as well as premonitory experiences demonstrated an improvement after Δ^9-THC treatment but results did not reach statistical significance (table 1).

We analyzed our data once again including only those patients who had received either 7.5 or 10.0 mg Δ^9-THC ($n = 8$). Using the TSSL ($p = 0.036$) and the subscore MT (YGTSS, $p = 0.036$) we found a significant improvement after Δ^9-THC treatment. Using the STSS ($p = 0.071$), the YGTSS ($p = 0.071$) and the subscores CMT (TSGS, $p = 0.071$) and MT (TSGS, $p = 0.071$) there was a trend towards a significant improvement.

On the Δ^9-THC treatment day 10 of 12 patients experienced a global

improvement (mean of +35% ± 28.0, range, 20 – 90%). Two patients noted no change (no. 7, 11). In contrast, on the placebo day only three patients (no. 6, 8, 10) reported a global improvement (mean of +7% ± 13.7, range, 10 – 40%) and nine felt no change. At the end of the study nine patients (no. 1, 2, 3, 4, 5, 8, 10, 11, 12) assessed the Δ^9-THC treatment day overall more positive than the placebo day (+43.3% ± 31.1, range, 10 – 100%). Three patients (no. 6, 7, 9) experienced the placebo day more positive (+21.7% ± 12.6, range, 10 – 35%).

No serious adverse reactions occurred. Blood pressure and pulse did not change significantly. After treatment with Δ^9-THC seven patients (no. 5, 7, 8, 9, 10, 11, 12) reported no side effects. Five patients (no. 1, 2, 3, 4, 6) experienced mild transient adverse reactions lasting for 1 – 6 hours (table 2). Two patients (no. 10, 11) reported mild side effects (headache) after placebo treatment.

Maximum plasma levels of THC were measured 30 (n=2), 90 (n=4) and 150 min (n=5) after medication (in one patient no level could be measured), of 11-OH-THC after 90 (n=5), 150 (n=6) and 240 min (n=1), and of THC-COOH after 90 (n=4), 150 (n=5) and 240 min (n=3). In 3 patients (no. 5, 8, 12) plasma concentrations of THC, 11-OH-THC and THC-COOH were already positive before treatment with Δ^9-THC indicating that these patients had used marijuana within the last 4-6 weeks before entering the study.

Simple linear regression analysis demonstrated a significant correlation between tic improvement (measured by STSS, TSGS, and YGTSS, respectively) and maximum plasma concentration of 11-OH-THC. Furthermore, there was a significant correlation between the oral dose of Δ^9-THC and the maximum plasma level of 11-OH-THC. When including only those nine patients exhibiting negative values before entering the study, in addition, there was a significant correlation between the oral Δ^9-

THC dose and the maximum level of THC-COOH (table 3). There was no correlation between plasma concentration of THC and its metabolites and changes in OCB after Δ^9-THC treatment.

Discussion

This pilot study is in line with previous results suggesting that cannabis sativa and Δ^9-THC have a beneficial influence on the symptoms of TS (5, 19, 20, 24). Our data demonstrated a significant reduction of motor and vocal tics and OCB using a self rating scale (TSSL). Using examiner ratings (STSS, TSGS and YGTSS) there was a significant improvement in the subscore CMT and a trend towards a significant improvement in MT, SVT and VT. We believe that global tic severity scores failed to reach statistical significance when using examiner ratings because examiner ratings are less sensitive to changes than a self rating scale (9, 10). A variety of clinical characteristics of TS make objective quantification of „disease severity“ difficult, like heterogeneity and complexity of tics, the waxing and waning course of the disease, and the possibility of voluntarily tic suppression (11). Even when performed under standardized conditions examiner ratings always are limited to an isolated and relatively brief time period.

Interpreting our data some aspects have to be taken into account. The sample size (n = 12) was relatively small. Nevertheless, 9 of 12 patients assessed that Δ^9-THC treatment was more successful than placebo treatment (mean global improvement = 43%). Due to the sample size we used a crossover design. However, the crossover effect was not significant indicating that a 4-week wash-out phase had prevented such an influence.

Because there was no previous experience in the therapy of TS with Δ^9-THC patients were treated only once with a single dose of Δ^9-THC. Hence, it was not possible to administer one exact dosage to each patient. Therefore, we analyzed our data once again but excluded those patients who had received a dosage of only 5.0 mg Δ^9-THC (n = 4). Although this sample included only eight patients data became

more robust suggesting that dosages of 7.5 and 10.0 mg Δ^9-THC, respectively, may be more effective in the therapy than lower doses.

Five patients experienced mild adverse effects. More significant side effects like headache, nausea, ataxia and anxiety were reported by those patients who had received 7.5 and 10.0 mg Δ^9-THC, respectively. However, only two out of seven patients who had used marijuana before reported about side effects but three out of five patients without prior use. Therefore, it can be speculated that side effects will decrease after a longer term treatment and will occur even less frequently when dosages are administered slowly.

It is well known that after oral administration Δ^9-THC absorption is slow, erratic and depends on the intake of food (8). Therefore, we correlated changes in clinical rating scales after Δ^9-THC treatment not only to the oral dose of THC but also to maximum plasma levels of Δ^9-THC and its metabolites 11-OH-THC and THC-COOH. In accordance with previous studies there was no correlation between clinical effects and plasma levels of Δ^9-THC (1, 16, 17). However, we found a highly significant correlation between maximum plasma levels of 11-OH-THC and all used examiner ratings suggesting that clinical improvement in TS may be caused by this highly active metabolite. Accordingly previous studies found after oral dosing – in contrast to administration by intravenous and smoking routes - high plasma concentrations of 11-OH-THC (27, 28). Furthermore, it has been suggested that after oral administration 11-OH-THC exerts significant clinical effects on the central nervous system (4, 13, 14, 25).

Since central cannabinoid CB1 receptors have been found to be located with high concentrations in the output nuclei of the basal ganglia it has been suggested that cannabinoids regulate motor activity (6, 15). There is much evidence that a

general role of the endogenous cannabinoid transmission is the manipulation of other transmitter systems predominantly to limit the extent of glutamate activation and GABA inhibition (2, 23). Furthermore, cannabinoid receptors are co-localized with dopamine receptors suggesting that cannabinoids influence dopaminergic processes (6, 15).

Our results suggest that in TS clinical effects of cannabis sativa and Δ^9-THC are due to a specific action on CB1 receptors and do not support the hypothesis that beneficial effects are due to unspecific mechanisms like sedation, reduction of anxiety or the fact of using an illegal drug. Furthermore, we hypothesize that the endogenous cannabinoid system might be involved in TS pathology. Interestingly, neuroanatomical structures which are probably involved in TS pathology are heavily associated with the CB1 receptor system. Considering an involvement of the dopamine system in TS pathophysiology it can be speculated that tic improvement might be caused by an interaction between cannabinoid and dopamine mechanisms. However, it also can be hypothesized that cannabinoids might influence motor control and behavior by modulating other transmitter system like GABA, glutamate, and serotonin.

In conclusion, our data suggest that a single-dose treatment with Δ^9-THC is effective and safe in the therapy of tics and OCB in TS. However, due to the small sample size and lack of experiences in the treatment of TS with Δ^9-THC this study was conducted as a crossover trial using a single-dose treatment. Therefore, results should be interpreted as preliminary. To confirm these data a prospective, double-blind, placebo-controlled follow-up study is needed involving a longer term therapy and a larger sample size.

Table 1: Changes in global tic scores and subscores after treatment with Δ^9-THC and placebo are summarized. Medians and mean scores ± SD of 12 patients are given. t = treatment effect

tic score	Δ^9-THC			Placebo			t
	median	Mean	±SD	median	Mean	±SD	p
STSS	**-1.0**	**-1.00**	**1.00**	**0**	**-0.33**	**0.65**	**0.132**
TSGS	**-7.5**	**-10.00**	**8.61**	**0**	**-3.50**	**7.53**	**0.132**
-SMT	-3.5	-4.25	3.91	0	-2.25	4.18	0.310
-CMT	-1.0	-2.08	2.94	0	0	0	0.015
-MT	-5.0	-6.25	5.19	0	-2.25	4.18	0.065
-SVT	-1.5	-2.50	2.43	0	-1.33	4.62	0.093
-CVT	0	-1.67	2.08	0	-0.08	0.29	0.132
-VT	-2.5	-3.67	3.89	0	-1.42	4.60	0.093
YGTSS	**-6.0**	**-10.25**	**12.95**	**0**	**-3.75**	**9.12**	**0.132**
-MT	-3.5	-3.42	3.85	0	-1.50	2.75	0.180
-VT	-2.0	-2.42	2.78	0	-0.58	1.16	0.093
TSSL	**-12.5**	**-14.00**	**10.97**	**-2.5**	**-4.92**	**6.69**	**0.015**
-SMT	-3.0	-5.67	5.69	-0.5	-2.00	3.16	0.026
-CMT	-3.0	-3.58	2.84	-0.5	-1.25	1.66	0.015
-MT	-6.5	-8.50	6.57	-1.5	-2.75	3.41	0.026
-SVT	-1.5	-3.08	4.01	0	-1.42	3.06	0.180
-CVT	-1.0	-1.58	1.93	0	-0.25	0.62	0.041
-VT	-4.5	-3.83	3.69	0	-1.58	3.03	0.132
-PE	-1.5	-2.17	2.25	0	-0.75	2.38	0.132
-impulsivity	-3.5	-3.33	3.45	-0.5	-1.42	2.11	0.093
-anxiety	0	-0.25	0.45	0	-0.17	0.39	0.589
-depression	-0.5	-0.58	0.67	0	-0.25	0.45	0.310
-ADHD	-0.5	-1.25	2.14	0	-0.25	0.87	0.093
-OCB	-3.5	-4.83	5.59	0	-1.33	2.50	0.041

Table 2: Adverse events after Δ^9-THC treatment in 5 patients are summarized. In addition, the particular dosages of Δ^9-THC are given and whether patients had prior use of marijuana.

patient no	dosage [mg Δ^9-THC]	adverse events	prior use of cannabis sativa
1	10	headache, nausea	occasionally (for the last time 2 weeks ago)
2	7.5	dizziness, hot flush	occasionally (for the last time 3 years ago)
3	7.5	dizziness, anxiety, tremble, sensitivity to noise and light, dry mouth, ataxia	no
4	5	tiredness, poor powers of concentration	no
6	5	tiredness, cheerfulness	no

Table 3: Correlation between oral dose of THC, maximum plasma concentration of THC and its metabolites 11-OH-THC and THC-COOH and changes in clinical rating scores.

* indicates that only patients are included demonstrating negative plasma values before treatment with Δ^9-THC (n=9).

	oral dose of THC	**TSSL**	**STSS**	**TSGS**	**YGTSS**
oral dose of THC		r=0.035 (n.s.)	r=0.364 (n.s.)	r=0.529 (p=0.077)	r=0.279 (n.s.)
THC	r=0.526 (p=0.079)	r=0.203 (n.s.)	r=0.057 (n.s.)	r=0.017 (n.s.)	r=0.114 (n.s.)
THC*	r=0.476 (n.s.)	r=0.307 (n.s.)	r=0.215 (n.s.)	r=0.523 (n.s.)	r=0.383 (n.s.)
11-OH-THC	r=0.691 (p=0.013)	r=0.062 (n.s.)	r=0.754 (p=0.005)	r=0.674 (p=0.016)	r=0.764 (p=0.004)
11-OH-THC*	r=0.866 (p=0.003)	r=0.187 (n.s.)	0.780 (p=0.013)	r=0.694 (p=0.038)	r=0.845 (p=0.004)
THC-COOH	r=0.389 (n.s.)	r=0.010 (n.s.)	r=0.045 (n.s.)	r=0.108 (n.s.)	0.130 (n.s.)
THC-COOH*	r=0.673 (p=0.047)	r=0.273 (n.s.)	r=0.551 (n.s.)	r=0.322 (n.s.)	r=0.448 (n.s.)

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