Effect of Sublingual Application of Cannabinoids on Intraocular Pressure: A Pilot Study

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Purpose: The purpose of this study was to assess the effect on intraocular pressure (IOP) and the safety and tolerability of oromucosal administration of a low dose of delta-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD).

Patients and Methods: A randomized, double-masked, placebo-controlled, 4 way crossover study was conducted at a single center, using cannabis-based medicinal extract of Δ-9-THC and CBD. Six patients with ocular hypertension or early primary open angle glaucoma received a single sublingual dose at 8 AM of 5 mg Δ-9-THC, 20 mg CBD, 40 mg CBD, or placebo. Main outcome measure was IOP. Secondary outcomes included visual acuity, vital signs, and psychotropic effects.

Results: Two hours after sublingual administration of 5 mg Δ-9-THC, the IOP was significantly lower than after placebo (23.5 mm Hg vs. 27.3 mm Hg, $P = 0.026$). The IOP returned to baseline level after the 4-hour IOP measurement. CBD administration did not reduce the IOP at any time. However, the higher dose of CBD (40 mg) produced a transient elevation of IOP at 4 hours after administration, from 23.2 to 25.9 mm Hg ($P = 0.028$). Vital signs and visual acuity were not significantly changed. One patient experienced a transient and mild paniclike reaction after Δ-9-THC administration.

Conclusions: A single 5 mg sublingual dose of Δ-9-THC reduced the IOP temporarily and was well tolerated by most patients. Sublingual administration of 20 mg CBD did not reduce IOP, whereas 40 mg CBD produced a transient increase IOP rise.

Key Words: delta-9-tetrahydrocannabinol, cannabidiol, glaucoma, IOP

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Glaucoma is one of the leading causes of blindness in the world. A range of medical and surgical options for glaucoma is currently available but treatment efficacy is variable and side effects can occur. Thus, the search for new therapeutic alternatives continues.

Cannabis and its derivatives are known to have therapeutic potential in a range of medical conditions.[1] Hepler and Frank[2] reported in 1971 the intraocular pressure (IOP)-lowering effect of smoking marijuana in a small number of subjects. Since these early observations numerous studies have been conducted confirming that different cannabinoids, including delta-9-tetrahydrocannabinol (Δ-9-THC), cannabidiol (CBD), cannabigerol, endogenous cannabinoids, and some synthetic cannabinoids, can reduce the IOP when administered systemically and topically.[3–12]

In glaucoma, the final pathway leading to visual loss is the selective death of retinal ganglion cells through apoptosis.[13] Substances that prevent apoptosis and inhibit retinal ganglion cell death could have a therapeutic benefit in glaucoma. Recent studies have documented the neuroprotective properties of cannabinoids independent of their effect on IOP.[14–20]

The best possible route for the administration of cannabinoids is also under investigation. Although smoking marijuana is an extremely efficient way of delivering cannabinoids, this form of administration cannot be justified in a medicinal context on ethical, medico-legal or safety grounds.[21] In addition to the acute side effects, the dose is difficult to control, long-term cannabis smoking is associated with emphysemalike lung changes and a possible increased frequency of lung cancer. Oral administration of cannabinoids has been evaluated.[3] However, the very low water solubility of key cannabis constituents aggravates still further the normal variability of absorption from the gastro-intestinal tract, resulting in poor predictability of both the timing and the intensity of peak effects. This is an important consideration given the wide variation in individual sensitivity to both the therapeutic and unwanted effects of cannabis derivatives and thus making this route undesirable. An additional drawback to the oral route is the conversion of the ingested form to larger quantities of THCs primary metabolite, the reputedly psychoactive 11-OH-Δ-9-THC.[22] For glaucoma patients topical administration of cannabinoids would be ideal, but presents pharmaceutical challenges that have yet to be overcome.[23,24]

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TABLE 1. Clinical Data of the Study Patients

Patient	Diagnosis R/L	Visual Field Defect	Glaucoma Therapy at Screening
1	Ocular hypertension both eyes	None	None
2	Primary open angle glaucoma both eyes	None	Timolol both eyes
3	Primary open angle glaucoma both eyes	None	Latanoprost both eyes
4	Ocular hypertension both eyes	None	None
5	Primary open angle glaucoma both eyes	Mild arcuate scotoma	Timolol 0.5% and latanoprost both eyes
6	Ocular hypertension both eyes	None	None

A number of alternative delivery methods for whole plant extracts are in development, including vaporizers, nebulizers, and an oromucosal spray. The latter was selected for this study because it has been shown to have a satisfactory pharmacokinetic profile[25] and has been well tolerated in clinical studies.[26]

In a therapeutic context whole plant extracts of cannabis may have advantages over single chemical entities such as Δ-9-THC. Herbs contain many active ingredients. Primary active ingredients may be enhanced by secondary compounds, which act in beneficial synergy. Other herbal constituents may mitigate the side effects of dominant active ingredients.[27] The purpose of this pilot study was to assess the effect on IOP of 3 whole plant cannabis-based medicinal extracts (CBME) containing a low dose of Δ-9-THC or CBD administered via a sublingual spray. A secondary objective was to assess the safety and tolerability of CBME, and in particular the occurrence of systemic and ocular side effects.

MATERIALS AND METHODS

The study population consisted of 6 patients with ocular hypertension or early primary open angle glaucoma with mild visual field defect (MD < 6 dB) and untreated IOP of > 24 and < 36 mm Hg in at least one eye. The patients were required to interrupt their topical glaucoma therapy and complete a wash-out period of 4 to 6 weeks before enrolment in the study. The conventional glaucoma therapy ceased for the entire duration of the study.

The study consisted of a baseline visit, 4 treatment visits, and 1 final visit each separated by 1 week. At the treatment visits, the patients received a single dose of the study treatment at 8 AM as allocated by a randomization schedule (see below). Each dose was applied sublingually by means of a pump-action oromucosal spray with a 100 μL actuator valve in 4 actuations at 5 minutes intervals. Patients were instructed not to swallow but to allow the drug to be absorbed from under the tongue. Patients received standardized extracts of 5 mg of Δ-9-THC, 20 mg of CBD, 40 mg of CBD, or placebo supplied by GW Pharmaceuticals, Salisbury, UK. Standard extracts of CBD contained a small amount of Δ-9-THC (1:21, 1 mg of Δ-9-THC and 21 mg of CBD).

The study protocol was approved by the local Research Ethics Committee and all patients gave written informed consent according to the Declaration of

TABLE 2. Summary of IOP by Time Point and Treatment

		Treatment			
Time Point (h)	Statistic	THC 5 mg	CBD 20 mg	CBD 40 mg	Placebo
0	n	6	6	6	6
	Mean	27.38	28.08	27.58	27.38
	Standard deviation	3.64	2.96	3.22	4.40
1	n	6	6	6	6
	Mean	26.29	28.29	27.92	26.83
	Standard deviation	3.92	4.50	6.01	5.50
2	n	6	6	6	6
	Mean	23.50	26.46	26.29	26.25
	Standard deviation	4.40	5.09	5.89	5.98
3	n	6	6	6	6
	Mean	23.58	24.08	24.42	23.50
	Standard deviation	5.72	3.34	5.22	5.01
4	n	6	6	6	6
	Mean	23.33	23.79	25.92	23.21
	Standard deviation	4.68	3.12	4.85	5.37
6	n	6	6	6	6
	Mean	20.83	22.38	22.50	22.25
	Standard deviation	4.20	2.68	4.64	4.25
12	n	6	6	6	6
	Mean	21.63	22.33	21.96	22.21
	Standard deviation	4.11	4.82	4.43	4.38

TABLE 3. Treatment-related Adverse Events

	THC 5 mg	CBD 20 mg	CBD 40 mg	Placebo
Subjects with at least 1 AE	3 (50%)	2 (33%)	5 (83%)	2 (33%)
Oral pain/discomfort	1 (17%)	0	3 (50%)	1 (17%)
Diastolic pressure ↑	0	2 (33%)	0	1 (17%)
Dizziness	1 (17%)	1 (17%)	0	0
Pharyngitis	0	0	2 (33%)	0
Bad taste	0	0	1 (17%)	0
Disturbed attention	0	1 (17%)	0	0
Feeling hot	0	0	1 (17%)	0
Headache	0	0	0	1 (17%)
Hypoaesthesia	0	0	0	1 (17%)
Hypotension	1 (17%)	0	0	0
Nausea	1 (17%)	0	0	0
Panic	1 (17%)	0	0	0
Photopsia	1 (17%)	0	0	0
Throat irritation	0	0	1 (17%)	0

Helsinki, World Medical Association. The study was conducted in a double-masked manner. The IOP measurements were obtained by the same investigator (I.T.) using a Goldman applanation tonometry. IOP was measured before dosing, and at 1, 2, 3, 4, 6, and 12 hours after treatment. At each time point, 2 IOP measurements were taken. If there was a difference of more than 2 mm Hg between readings, a third measurement was taken. The IOP data used for analysis was the average of the readings at each time point. Vital signs [blood pressure (BP), heart rate] were evaluated before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 12 hours after dose. Best-corrected early treatment of diabetic retinopathy study visual acuity was obtained before treatment and at 2.5 and 12 hours after dose. Visual field testing was performed using quantitative automated perimetry (Humphrey visual field analyser, Carl Zeiss Meditec, Dublin, CA) with the Swedish interactive threshold algorithm-fast program 2 hours after dosing.

For statistical analysis, *t* tests for paired samples were used to assess the effect of the CBMEs compared with placebo. *P* values ≤ 0.05 were regarded as statistically significant.

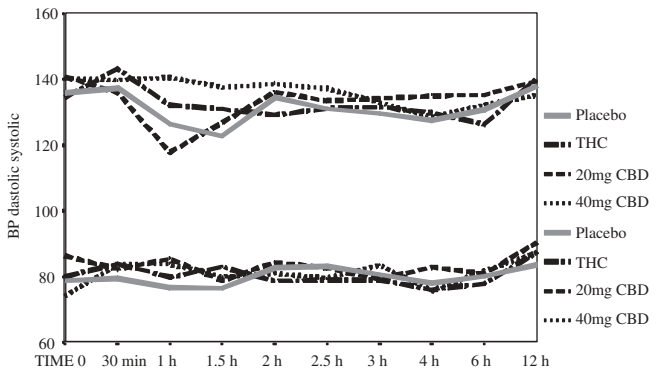

FIGURE 1. Changes in systolic (top) and diastolic (bottom) BP (mm Hg) after sublingual administration of placebo, Δ-9-THC (5 mg) and CBD (20 and 40 mg).

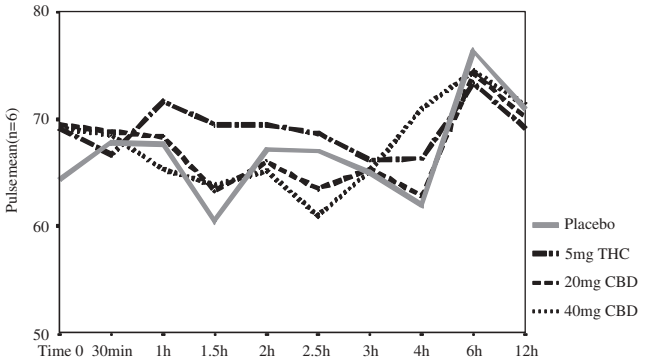

FIGURE 2. Changes in heart rate (beats per minute) after sublingual administration of placebo, Δ-9-THC, and CBD.

RESULTS

Clinical details of the 6 subjects enrolled in the study are shown in Table 1. All subjects were male with a mean age of 55.3 (SD = 5.0) years. Effects on IOP (average of both eyes per patient) are shown in Table 2. Two hours after sublingual treatment with 5 mg Δ-9-THC, the IOP was lower (23.5 mm Hg) than after placebo administration (27.37 mm Hg, $P = 0.026$). CBD administration did not reduce the IOP with either of the 2 doses studied. In fact, 4 hours after administration of 40 mg CBD, the mean IOP was higher than following administration of placebo (25.92 mm Hg vs. 23.21 mm Hg, $P = 0.028$).

Adverse events are shown in Table 3. There were no serious or severe adverse events, and all but 2 (nausea and hypotension after administration of 5 mg THC, rated moderate) were rated mild. No sleepiness and giddiness was observed. The effects of the different CBMEs and placebo on the BP are displayed in Figures 1 and 2. With the 40 mg of CBD treatment, the mean systolic BP increased slightly after 60 and 90 minutes ($P = 0.024$ and 0.014, respectively). The heart rate 90 minutes after treatment with 5 mg Δ-9-THC was faster than with placebo ($P = 0.027$). Other variables and measurements did not change. Visual acuity and visual field examinations were not influenced by the CBMEs (data not shown).

DISCUSSION

Although cannabis is the most commonly used illegal drug in the UK, cannabinoids have potential medicinal benefits.[1] Some formulations are already available for medical use, dronabinol (Marinol, synthetic Δ^9-tetrahydrocannabinol) and nabilone in the UK and Sativex in Canada. They are administered orally to treat emesis and as appetite-stimulants for chemotherapy patients.[1]

The potential use of cannabinoids in glaucoma has been explored since the 1970s. However, several challenges emerged, including the psychotropic side effects (eg, euphoria, dysphoria, disruption of short-term

memory), lowering of arterial BP, and variable oral absorption. Topical application has been associated with irritation and corneal damage.[23,24]

In this study, a very low dose of Δ-9-THC in the form of a whole plant extract was used to try to minimize the known side effects associated with higher doses. A novel formulation applied sublingually was used. Overall, the treatment appeared to be well tolerated, with only one patient experiencing mild psychotropic side effects. The results confirm previous findings indicating a modest IOP-lowering effect. The IOP reduction caused by Δ-9-THC is known to be dose-dependent and temporary. It is possible that sustained dosing over a period of weeks may have had a more positive effect. Human and laboratory studies of various cannabinoids given systemically or locally found a substantial IOP reduction of 25% to 30%.[3–12] The mechanism of action by which cannabinoids lower the IOP is not yet fully understood. Strong CB_1 receptor labeling has been detected in the ciliary epithelium, strong-to-moderate levels in the trabecular meshwork and Schlemm's canal, whereas in the ciliary muscle and the ciliary body vessels there was moderate labeling evident,[28–30] suggesting that cannabinoids may influence the aqueous humor production and outflow. The time-lag in achieving IOP reduction was presumably related to the time taken for the THC to reach the intraocular cannabinoid receptors after the sublingual application.

To our knowledge, this is the first study evaluating the effect of CBD on IOP in humans. A single 20 mg or 40 mg sublingual dose of CBD did not have an IOP-lowering effect. At the 40 mg dose CBD the IOP and the systolic BP were slightly raised. No psychotropic side effects were detected in patients treated with CBD.

An attribute which has stimulated new interest in the possible therapeutic application of cannabinoids in glaucoma is their possible neuroprotective potential.[13] Several cannabinoids have shown this beneficial effect, including CBD and Δ-9-THC.[14–20] The mechanisms underlying the neuroprotective effect are still under investigation, but may include inhibition of glutamate acid release by increasing K^+ and decreasing Ca^{2+} permeability, blockage of NMDA receptors, and antioxidant activity.[12] In experimental studies by Braida et al,[19] CBD was effective in antagonizing postischemic changes, and El-Remessy et al[20] found both Δ-9-THC and CBD to have a neuroprotective effect in a rodent model of glaucoma.

In summary, this study confirmed the IOP-lowering effect of Δ-9-THC when delivered by a novel sublingual route. The modest reduction of IOP associated with the low dose of Δ-9-THC used in this trial is not likely to be clinically relevant. Administration of CBD in 2 different doses did not show the same effect on IOP. Sublingual administration of cannabinoids was well tolerated. Further research on the potential value of sublingual administration of cannabinoids for glaucoma would be desirable.

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