DELTA-9-TETRAHYDROCANNABINOL (THC) IN THE TREATMENT OF END-STAGE OPEN-ANGLE GLAUCOMA

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ABSTRACT

Purpose: Evidence exists that the administration of cannabinoid derivatives can lower intraocular pressure. Some patients with glaucoma believe they are being deprived of a potentially beneficial treatment. Therefore, the Research Advisory Panel of California instituted the Cannabis Therapeutic Research Program to permit compassionate access to cannabinoid derivatives. Data about the potential therapeutic usefulness and toxicity of these agents were collected. This study reviews the results of this program with the specific aim of providing further direction for these investigational efforts.

Methods: A survey of local ophthalmologists indicated an impressive interest in participating in and contributing patients with glaucoma unresponsive to treatment to this study. Appropriate patients were treated with either orally administered delta-9-tetrahydrocannabinol capsules or inhaled marijuana in addition to their existing therapeutic regimen.

Results: Although 20 ophthalmologists were approved as investigators, only nine patients were enrolled in the study. An initial decrease in intraocular pressure was observed in all patients, and the investigator's therapeutic goal was met in four of the nine patients. However, the decreases in intraocular pressure were not sustained, and all patients elected to discontinue treatment within 1 to 9 months for various reasons.

Conclusions: This uncontrolled, unmasked, nonrandomized study does not permit definitive conclusions about the efficacy or toxicity of cannabinoids in the treatment of glaucoma. There is an impression that this treatment can lower intraocular pressure, but the development of tolerance and significant systemic toxicity appears to limit the usefulness of this potential treatment. Both patients and ophthalmologists greatly appreciated the opportunity to participate in this study.

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INTRODUCTION

The hemp plant, or *Cannabis sativa*, provides leaves and flowering parts that, when dried, result in a complex pharmacologic mixture called marijuana. Hashish is the sticky resin that is secreted by the plant in hot, dry weather. These mixtures contain 420 natural products, including 28 natural cannabinoids.[1] The cannabinoids share several pharmacologic actions, including intraocular pressure (IOP)–lowering effects, central nervous system effects, and cardiovascular system effects.[2-6]

The Research Advisory Panel of California was created in 1969 by the California Legislature to encourage research into the nature and effects of abused drugs, to review and approve research involving controlled substances, and to function as a human subject's protection committee in research involving controlled substances. Subsequently, the legislature became concerned that the status of marijuana as a stringently regulated drug might be inhibiting research into its possible therapeutic effects. Therefore, in 1979, the Cannabis Therapeutic Research Program was established to provide compassionate access for patients to marijuana or delta-9-tetrahydrocannabinol (THC) as a potential treatment for nausea and vomiting associated with cancer chemotherapy.

Evidence exists that the administration of cannabinoid derivatives can lower IOP in normal and glaucomatous eyes.[2,7] As a consequence, some patients with glaucoma believe that they are being deprived of a potentially vision-saving treatment and are using marijuana illegally and, in many cases, without medical supervision. Therefore, in 1984, the California legislature, by way of the Research Advisory Panel and its ongoing Cannabis Therapeutic Research Program, added to its mandate and permitted compassionate access for appropriate glaucoma

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patients to these cannabinoid derivatives. This study allowed the collection of preliminary data about the potential therapeutic usefulness and toxicity of THC and marijuana in the treatment of end-stage open-angle glaucoma. This program was effectively ended in October 1986 when THC was marketed as dronabinol (Marinol), making the availability of free THC unnecessary. This presentation reviews the data collected during this 2-year study with the specific aim of providing direction for further investigational efforts within this area of clinical and laboratory research.

METHODS

A 1984 survey of ophthalmologists practicing within California indicated an impressive interest in contributing patients with glaucoma unresponsive to available treatment to a study permitting access to cannabinoid derivatives. Subsequently, a protocol was designed with the goal of permitting appropriate patients to receive treatment with either orally administered THC capsules or inhaled marijuana in addition to their existing therapeutic regimen.[8]

INVESTIGATORS

California ophthalmologists certified by the American Board of Ophthalmology could apply to become an investigator. Following application, the potential investigator was required to complete a Food and Drug Administration investigator's form and agree to follow the Cannabis Protocol for Glaucoma. Participating investigators were required to assume full responsibility for determining that their patients conformed to the admission requirements. Continued participation was conditioned upon the investigator's complicance with the protocol, including adequate record keeping on treatment outcome and timely submission of data forms to the Panel.

EXPERIMENTAL SUBJECTS

A Patient Qualification Review Board appointed by the Research Advisory Panel reviewed all of the paperwork, including the patient's medical history and examinations, and referred the potential subject's material to the author for possible enrollment. The author approved a patient as an experimental subject following a lengthy discussion with the investigator and the patient to determine whether the patient met the qualifications to enter the study. Thereafter, the patient was elgible to enroll in the study and receive THC or marijuana cigarettes from an approved pharmacy within the area.

DESIGN OF STUDY

This study was designed as an uncontrolled, unmasked, nonrandomized, prospective evaluation of the effects of orally administered THC or smoked marijuana on IOP in subjects with uncontrolled IOP while receiving maximally tolerated conventional glaucoma treatment. If subjects began treatment with orally administered THC and the capsules appeared ineffective, the subject could switch to marijuana cigarettes. During the study, ancillary glaucoma medications could not be added or deleted while adjusting THC or marijuana doses without notifying the investigator.

EXCLUSION CRITERIA

A complete medical history and ocular examination were submitted for each patient to determine the patient's suitability for inclusion within this study. Patients were not accepted as subjects for the study if they met one or more of the following exclusion criteria: (1) glaucoma other than primary open-angle glaucoma; (2) occludable angles; (3) not on maximally tolerated medical therapy, including an attempt to use the parasympathomimetics, sympathomimetics, carbonic anhydrase inhibitors, and topically applied beta blockers; (4) uninformed about the proven potential therapeutic advantages of conventional glaucoma surgeries, including laser trabeculoplasty; (5) younger than 18 years of age; (6) a history of any psychiatric disorder, unless approved by a psychiatrist; (7) women of childbearing age unless using a reliable method of birth control; (8) pregnant or nursing women; (9) significant cardiovascular problems, including unstable angina pectoris, cardiac arrhythmias, or hypotensive episodes; (10) a history of dysphoric reactions to marijuana; (11) suffering from senility; (12) unwilling to abstain from driving automobiles or operating machinery; (13) impaired pulmonary or hepatic function; (14) unwilling or unable to give informed consent for this study.

BASELINE HISTORY AND EXAMINATION

All subjects provided a baseline history and underwent examination to identify the presence of exclusion criteria. This included a history of glaucomatous progression and treatment, current medical management, a complete ocular examination, and the investigator's estimation of a maximum safe IOP level for protection of their optic nerves, which was then considered the goal of therapy. At the conclusion of the examination, if the patient was considered an appropriate subject for the study, the risks, benefits, and alternatives were explained to the subject, and informed consent to participate in the study was subsequently obtained.

INFORMED CONSENT

All subjects read, discussed, and signed the form entitled Consent to Be a Research Subject in the California Cannabis Therapeutic Progam. They were informed that the use of THC or marijuana for the treatment of

glaucoma is experimental and that there is no evidence showing that this treatment benefits open-angle glaucoma. Furthermore, they were informed about the potential risks of taking cannabinoid therapy, including changes in vision, hearing, mood, and muscle control; wheezing; decreased blood pressure; feeling faint, intoxicated, confused, nervous, or scared; and rapid heart beat, red eyes, dry mouth, daydreams, hallucinations, forgetfulness, decreased energy, sleepiness, and a distortion of perception. Subjects were warned that some of the effects may be pleasant or distressing in an unpredictable fashion and that they may persist for up to 24 hours. In addition, they were warned that marijuana cigarettes may be harmful to the lungs and have the potential to cause lung cancer, which can be lethal. They were told that they could not operate a car or any machinery while using these treatments because they would endanger themselves and others. Finally, alternative treatments, including different dose forms and higher concentrations of available medications and conventional surgery, were reviewed and clearly identified as proven and efficacious treatments well recognized to benefit glaucoma, unlike the experimental use of cannabis derivatives. In addition to signing the consent form, the subjects read and signed the Experimental Subject's Bill of Rights.

MEASUREMENT OF IOP

The subject's IOP was determined at baseline immediately prior to the start of cannabis therapy by applanation tonometry with three consecutive measurements. Thereafter, the subject's IOP was evaluated weekly, at the same time of day, until satisfactory control of IOP was achieved for 2 consecutive weeks. Satisfactory control of IOP meant a level of IOP that the investigator believed, as determined from prior experience with the subject, was safe for the health of the subject's optic nerve. When satisfactory IOP control was obtained for 2 consecutive weeks, the frequency of evaluation could be reduced to once a month. Treatment evaluation forms were returned to the Panel on a weekly basis and reviewed by the author.

TREATMENT EVALUATIONS

On subsequent visits, complete ocular examinations were performed with special attention to the subject's IOP and blood pressure, each measured at the same time of day at each visit. At the conclusion of the office visit, the investigator provided a clinical impression of the effectiveness of treatment since the last evaluation as follows: Improved, Same, Worsened, Uncertain. Cannabis side effects were recorded on both a treatment evaluation form by the investigator and a patient questionnaire by the subject.

PATIENT QUESTIONNAIRE

Subjects were required to complete a side effect and psychosocial function questionnaire for each week until their condition stabilized with a given dose of THC or marijuana. This form was submitted to the Panel and reviewed monthly along with the investigator's treatment evaluation form. Additional comments regarding treatment and coexistent side effects were encouraged from each subject at each evaluation period in an attempt to monitor side effects and possible excessive drug accumulation.

TREATMENT MEDICATIONS AND DOSING SCHEDULES

Oral THC and marijuana cigarettes were provided without charge by the National Cancer Institute and the National Institute on Drug Abuse and dispensed by approved pharmacies. The oral THC dosage forms consisted of soft gelatin capsules containing 2.5 mg or 5 mg of THC dissolved in sesame oil. Initial dosage for each patient was 2.5 mg or 5 mg given every 4 hours (four times daily) while awake. The dose was increased or decreased by 2.5-mg increments as needed to obtain a greater effect or less toxicity, with a maximum permitted dose of 20 mg four times daily. Marijuana cigarettes marked in quarters were supplied and contained 6 mg of THC. Subjects were requested to inhale one fourth of a cigarette every 3 hours (five times daily) while awake. They were instructed to inhale deeply, hold the inhalation for 5 seconds, and then exhale; after 10 seconds the cycle is repeated until the appropriate dose is smoked in approximately 5 minutes. A flameproof holder was used to permit delivery of all the cigarette dosage. This dose was increased or decreased as needed to provide a greater effect on IOP or less toxicity. Subjects could not use "street" marijuana during the study.

TERMINATION FROM STUDY

Subjects could withdraw from the study at any time for any reason. At the time of termination, the reason for discontinuing treatment (eg, toxic effects, lack of efficacy, too tedious, geographic change, ocular surgery, other, uncertain) was noted on the final evaluation form. No subject was permitted to use these medications for more than 12 months.

RESULTS

During this 2-year period, 20 ophthalmologists were approved as investigators and nine patients were enrolled into the study to received oral THC for 1 to 9 months. No subjects consented to receive smoked marijuana. The characteristics of these subjects with end-stage open-angle glaucoma are summarized in Table I. At the time of entry into the study, subjects had uncontrolled IOP despite using maximally tolerated medical treatment. Furthermore, the majority of subjects had a history of one or more glaucoma surgeries.

TABLE I: CHARACTERISTICS OF SUBJECTS

PATIENT NO. (SEX/AGE)	EYE	SNELLEN VISION (C/D)	VISUAL FIELD	SURGERY	MEDICATIONS
1. MT (M/77)	OD	HM (0.9)	Paracentral island	Laser	Methazolamide, 50 mg bid Epinephrine 2% bid
	OS	20/60 (0.9)	Severe constriction	Laser	Timolol 0.5% bid
2. WR (M/58)	OD	20/30 (0.9)	Severe constriction	Laser trabeculectomy	Acetazolamide, 250 mg qid Timolol 0.5% bid Propine bid Phospholine iodide 0.06% qd
	OS	HM (0.9)	5° field	Laser trabeculectomy, cyclocryotherapy	Pilocarpine 2% qid
3. NC (M/71)	OD	HM (0.9)	5° field	Laser trabeculectomy	Acetazolamide, 250 mg qid Timolol 0.5% bid
	OS	20/80 (0.9)	10° field	Laser trabeculectomy	Pilocarpine 2% qid Propine bid Phospholine iodide 0.06% qd
4. VD (F/60)	OD	LP (0.9)	Unable	Trabeculectomy	Acetazolamide, 250 md qid
	OS	HM (0.9)	Unable	Trabeculectomy, iridodencleisis	Timolol 0.5% bid Epinephrine 2% bid Pilocarpine 2% qid
5. DF (M/50)	OD	20/60 (0.9)	10° field	Laser	Acetazolamide, 250 mg qid
	OS	HM (0.9)	Unable	Laser	Timolol 0.5% bid Carbachol 0.75% bid
6. BF (M/70)	OD	LP (0.9)	5° field	Laser	Methazolamide, 50 mg bid
	OS	LP (0.9)	5° field	Laser	Carbachol 0.75% bid Timolol 0.5% bid Epinephrine 2% bid
7. CC (F/52)	OD	HM (0.9)	Severe constriction	Trabeculectomy	Acetazolamide, 250 mg qid Epinephrine 2% bid
	OS	NLP (0.9)	Unable	Trabeculectomy	Carbachol 0.75% bid Pilocarpine 2% qid
8. MK (M/60)	OD	HM (0.9)	5° field	Trabeculectomy	Acetazolamide, 250 mg qid
	OS	HM (0.9)	5° field	Trabeculectomy	Epinephrine 2% bid Timolol 0.5% bid Pilocarpine 2% qid
9. RG (M/38)	OD	Enucleated	Enucleated	Trabeculectomy, enucleation	Acetazolamide, 250 mg qid Timolol 0.5% bid
	OS	HM (0.9)	5° field	Trabeculectomy	Propine bid Phospholine 0.06% qd Pilocarpine 2% qid

C/D, cup-disc ratio.

An initial decrease in IOP was observed in all subjects. The therapeutic goal of the investigator was achieved in four of nine subjects, and six of nine were considered "improved" during at least one visit during their treatment (Table II). Subject D.F. was improved at every visit for a 9-month period. Subject C.C. was described as "improved" during more than 50% of the follow-up visits during his 5-month treatment. Both of these subjects were improved at the time of termination from the study, when each subject underwent cataract surgery. All of the other subjects appeared to have lost the beneficial effects of treatment on their IOP at the time of termination.

All subjects experienced toxic effects from oral THC during their treatment. Intolerable side effects forced four subjects to be terminated early from the study. These side effects and the corresponding dose of THC are summarized in Table III. No subject reported enjoying effects of THC related to the central nervous system. Subjects who did not tolerate THC were offered access to marijuana, but all of them declined.

TABLE II: INTRAOCULAR PRESSURES

PATIENT (DURATION TREATMENT)	INITIAL IOP* (GOAL IOP)	TREATMENT RANGE	CONSIDERED IMPROVED	MET GOAL
1. MT (14 wk)	19 (<12)	15-18	1 visit	No
2. WR (3 wk)	24 (<20)	20-24	Many visits	No
3. NC† (20 wk)	18-22 (<16)	14-17	2 visits	Yes†
4. VD (20 wk)	30-46 (<20)	28-40	Many visits	No
5. DF (36 wk)	19-25 (<16)	14-23	Every visit	No
6. BF (8 wk)	19-22 (<20)	15-20	3 visits	Yes
7. CC‡ (21 wk)	22-25 (<20)	16-20	More than 50% visits	Yes‡
8. MK (20 wk)	17-21 (<10)	15-16	Many visits	No
9. RG§ (28 wk)	20-24 (<15)	11-15	Many visits	Yes§

*If IOP varied >2 mm Hg during three measurements, range given.
†Discontinued acetazolamide and propine during study.
‡Discontinued acetazolamide and carbachol during study.
§Possible increased compliance.

DISCUSSION

The identification of brain, ocular, and peripheral cannabinoid receptors in several different mammals, the cloning of cannabinoid receptors, and the discovery of anandamide, an endogenous cannabimimetic eicosanoid, has greatly augmented the study of cannabinoid pharmacology in recent years.[9-13] Some of these pharmacologic investigations have attempted to develop new drugs useful for the treatment of the glaucomas.[14-17] However, thus far none of these efforts have included the use of cannabinoids in glaucoma patients with advanced disease. Therefore, it seemed timely to present this study, which represents the largest series of end-stage glaucoma patients treated with a cannabinoid derivative thus far completed. The data collected during this study are presented with the aim of providing direction and encouragement for further investigational efforts within this area of clinical and laboratory research.

Because this is a small, uncontrolled, unmasked, nonrandomized, prospective study of short duration, it does not permit definitive conclusions about the efficacy of cannabinoids in the treatment of glaucoma. However, there is an impression from the data collected during this 2-year investigation that treatment with oral THC lowered IOP in some of this group of end-stage open-angle glaucoma patients. Following the initiation of THC treatment, all of the subjects demonstrated at least a transient improvement in the reduction of IOP (Table II). An improvement was noted during more than 50% of the office visits in two of the nine enrolled subjects. In fact, one of the subjects was considered improved on all of the follow-up visits over a 36-week treatment period despite the fact that he never met the goal of treatment which the investigator considered ideal. The therapeutic goal of the investigator was achieved in four of nine subjects. Subjects N.C and C.C. each demonstrated an improved IOP control while using 5 mg of THC four times daily despite discontinuing coexistent carbonic anhydrase inhibitors and parasympathomimetics or sympathomimetics. Unfortunately, many of the subjects appeared to develop a tolerance to THC because their IOPs increased during the latter period of their treatment. Of course, as with any uncontrolled study, the observed improvements in IOP control may have been related to enhanced compliance associated with a subject's participation in the study or the added attention or encouragement given to the subject during the treatment period. This appeared to be the case with at least one subject (R.G.), in the opinion of the investigator, as indicated in Table II.

All subjects experienced side effects during their treatment with THC during this study (Table III). The most commonly described toxic effects were dry mouth, sleepiness, dizziness, depression, and confusion; these effects were the same as those reported by other investigators.[18,19] Although many of the side effects were considered mild and were of little concern to subjects, other effects were very significant. For example, the reason for

TABLE III: SIDE EFFECTS WITH THC TREATMENT

PATIENT (DURATION TREATMENT)	DOSAGE AND SIDE EFFECTS				REASON FOR TERMINATION
1. MT (14 wk)	5 mg qid: mod dizzy → mild sleepy mod light-headed mild confusion	5 mg qid: mild dizzy → mild sleepy	7.5 mg qid: mild dry mouth mod dizzy → mild sleepy	7.5 mg qid: mild dizzy	Lack efficacy
2. WR (3 wk)	2.5 mg qid: severe dizzy severe anxiety severe depression mod confused severe distortion of perception				Side effects
3. NC* (20 wk)	5 mg qid: mod dry mouth mod sleepy → mild dizzy mod sedation	5 mg qid: mild dry mouth mild sleepy weight increase			Side effects (weight increase)
4. VD (20 wk)	5 mg qid: mild dry mouth mild depression/elation → mod sleepy mild distortion of perception	15 mg qid: mod dry mouth mod dizzy mod confusion mod sleepy mod distortion of perception			Side effects
5. DF† (36 wk)	5 mg qid: mild dry mouth → mild dizzy	7.5 mg qid: mild dry mouth mod dizzy	15 mg qid: mild dry mouth mod dizzy	17.5 mg qid: mod dry mouth mild dizzy	Cataract surgery
6. BF (8 wk)	5 mg qid: mild anxiety mild sleepy mild light-headed mild elation	7.5 mg qid: severe dizzy mod anxiety mild dry mouth mild sedation mild depression mild confusion			Side effects
7. CC* (21 wk)	2.5 mg qid: mild anxiety mild elation mild dizzy mild light-headed mild dry mouth mild confusion (last 3 gone in several weeks)	5 mg qid: mod dry mouth mod dizzy mod light-headed (all gone in several weeks)			Cataract surgery
8. MK* (20 wk)	2.5 qid: mild dry mouth mild dizzy → mild depression mild sedation	2.5 qid: mild dry mouth mild dizzy			Change ophthalmologist
9. RG* (28 wk)	2.5 mg qid: mild dry mouth mild depression → mild sleepy	2.5 qid: mild dry mouth mild sleepy			Too tedious

*Possible tolerance to side effects.
†By 30th week, no side effect on 17.5 mg qid.

termination from the study for four of the nine subjects was intolerable side effects, such as distortion of perception, confusion, anxiety, depression, and severe dizziness. Changes in blood pressure have been reported with THC treatment.[20,21] Therefore, blood pressures were measured and the symtoms of systemic hypotension were carefully searched for at each visit. The dizziness and light-headedness reported by subjects in this study were never associated with systemic hypotension.

In most cases, the therapeutic benefit did not outweigh the toxicity associated with treatment as percieved by the subject. For example, one subject (N.C.) was unhappy because he gained weight while enrolled in the study. It was unclear whether his enhanced appetite was related to discontinuing acetazolamide or the concurrent use of THC. In any case, he was upset enough about this apparent effect that he withdrew from the study despite an improvement in IOP control and his ophthalmologist's opinion that he had met the goal of treatment. His termination from the study was considered to be due to intolerable side effects of THC.

Although the literature is unclear about the development of tolerance to the effects of cannabinoid administration, there was some evidence for tolerance in this study. There appeared to be a tendency for the beneficial effects on IOP to outlast the side effects in some patients, as demonstrated in Table III and as has been previously reported.[22] Unfortunately, there also appeared to be a tendency for tolerance to the beneficial IOP effects to develop in most of the subjects, as summarized in Table II.

A major limitation for applying the results of this study to present-day glaucoma therapy is that this study was completed in 1986, before many of the glaucoma medications currently in use were available. More specifically, prostaglandin derivatives, topically applied carbonic anhydrase inhibitors, and relatively alpha$_2$-specific sympathomimetics were not commercially available during the 1980s. It is possible that if THC were added to the current therapeutic regimen of maximally tolerated therapy during the treatment of end-stage glaucoma, it would provide a less optimistic impression of its therapeutic usefulness.

Throughout the study, there was no observed tendency for either the physicians or the patients to abuse their access to cannabinoid derivatives. In fact, none of the subjects appeared to enjoy the psychotropic effects of THC. This is consistent with the observation made in previous studies that the environment, expectations, and reason for use of individuals during cannabinoid administration influence the overall personal experience and psychologic reaction to the effects of the cannabinoids following their administration.

Finally, it was clear that both the patients and ophthalmologists greatly appreciated the opportunity to participate in this study. The program not only provided patients with legal and compassionate access to cannabinoid treatment as a last-resort treatment during the the management of end-stage glaucoma unresponsive to conventional treatments, but it provided an opportunity for careful monitoring and extensive education of all of the patients interested in this potential treatment. Therefore, this opportunity greatly increased the safety for all of the patients who participated as subjects and even the patients who did not qualify for treatment because they were misinformed about the lack of proven value for the treatment or were ignorant of the potential dangers of taking cannabinoids in an attempt to lower IOP.

CONCLUSIONS

This uncontrolled, unmasked, nonrandomized, prospective study does not permit definitive conclusions about the efficacy or toxicity of cannabinoids in the treatment of glaucoma. There is an impression from this study that treatment with oral THC lowered IOP in this group of patients with end-stage open-angle glaucoma, but the development of tolerance and the coexistence of significant systemic toxicity limited the potential usefulness of this treatment. It was particularly impressive to the investigators that throughout the study there was no observed tendency for either the physicians or the patients to abuse their access to cannabinoid derivatives. Furthermore, both the patients and ophthalmologists greatly appreciated the opportunity to participate in a study that gave them legal access to cannabinoids as a last-resort treatment for end-stage glaucoma unresponsive to conventional treatments.

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DISCUSSION

DR DOUGLAS R. ANDERSON. Thanks to Dr Flach for this lucid and straightforward report. To summarize the main conclusions, the author expressed surprise that fewer subjects enrolled than had been expected, despite well-known and continued public interest in use of cannabinoids for medical purposes, including glaucoma. Perhaps a good part of the public fascination is in possible use this drug in ordinary cases of glaucoma as an alternative to already available therapy. The types of cases recruited for this study were severe cases not adequately controlled with any other treatment options, and in these cases THC was inadequately effective or impractical because of side effects.

It is, however, known that THC will lower the IOP, and that there are receptors in both the trabecular meshwork and the ciliary body. A few decades ago, I had a young patient who knew I could not prescribe marijuana for him. Having recently opened a business, he had some projects to get under control before he could proceed with the surgery I had recommended, and he asked me to monitor his IOP frequently while waiting. The readings were variable, and he revealed that on some days, at various intervals before the measurements, he had smoked marijuana. He had kept a diary of times and pressures, and also noted the quality of the particular marijuana he had smoked on each occasion, judged from the mental effects he enjoyed. From this he worked out a nice dose-response curve and the duration of the effect on IOP. I no longer remember the details, except that the effect was not long-lived and did not persist beyond the time he felt "high." The net result was that he could not focus on his work and simultaneously keep his IOP at the desired pressure level. Therefore he did undergo surgery, which worked well for him for the next several years during which he remained under my care.

At least for some patients, then, the side effects and short duration of action may simply outweigh the advantages compared to standard therapeutic options available. When patients ask about marijuana, that is exactly how I explain the situation—that THC may work to lower the IOP, but perhaps not more effectively than other available drugs, which have been better tested scientifically, have longer duration of action, and also have fewer side effects.

Do cannabinoids have a place at all? Dr Paul Palmberg has one patient under his care with glaucoma from childhood who has had all known medications, some not tolerated, and others not fully effective. The patient has had several operations, the most recent with the complication of a postoperative suprachoroidal hemorrhage, so further surgery has been avoided. The IOP can be brought from 50 mm Hg to 25 mm Hg with either timolol or marijuana, but in combination to 15 mm Hg. The patient has used marijuana in this manner for a couple of decades now. Newer alpha-adrenergic agents and prostaglandin analogues have not been satisfactory substitutes. Because of the short duration of action, this treatment requires 10 NIDA-provided marijuana cigarettes per day and is thus not so convenient, but for this patient

it is the best alternative.

Based on the experience of this patient and of others reported to him, Dr Palmberg believes marijuana can be very effective when the IOP is quite high, but seems minimally effective in patients with modestly elevated or normal IOP. He also commented that with continual use, the lowering of blood pressure and the mental effects disappear, but the favorable effects on IOP persist, so some of the problems noted in acute or short-term studies may have underestimated the potential for this class of drugs.

Dr Palmberg participated in a NIDA-workshop cosponsored by NIH (Feb 1997) at which various potential medicinal uses of marijuana were discussed. Dr Paul Kaufman reviewed the then available studies with respect to glaucoma for the workshop, and most information dealt with acute or short-term experiments. The report of this workshop may provide those interested with a compendium of background information suggesting a potential not yet proved or developed.

Presumably, physicians can legally prescribe dronabinol (Marinol) for glaucoma as an off-label use, although prior clearance from appropriate authorities might be wise. Within the past week a well-known entertainer was arrested at an airport checkpoint for possession of marijuana, which, it was claimed, was being used to treat glaucoma. There may thus be some unanalyzed experience with cannabinoids, although even if collected, scattered anecdotal information will not substitute for further properly designed studies of long-term clinical use such as the one conducted by Dr Flach. Continued interest in the class of compounds may be warranted if longer-acting forms can be developed, and if the undesirable effects are documented to disappear after several days so that patients can work effectively and drive safely. Of particular pharmacologic interest is that cannabinoids lower IOP through mechanisms independent of those of drugs currently on the market. The implication is that cannabinoids may work when other classes of drugs don't, and that it could be additive to other drugs.

DR GEORGE L. SPAETH. I obtained tetrahydrocannabinol in 1970 and manipulated it into a form that could be used as eye drops. Masking was attempted, using one eye as control, but the eyes on the tetrahydrocannabinol turned beet red. There was no effect on IOP when we compared the treated and untreated eyes. How does this drug work to lower pressure? Is it possible to develop some type of topical product that might limit the problem of the systemic side effects?

DR LOUIS B.CANTOR. Is there any understanding of the pharmacology, and do receptors for the cannabinoids exist? Since this drug appears to lower IOP, do we know anything about the mechanism? Is the mechanism similar to that of our other fatty acid lipid compounds that improve pressure-sensitive or pressure-insensitive outflow pathways?

DR ALLAN J. FLACH. Dr Anderson mentioned the fascination that has existed concerning this group of drugs. This interest has been present for over 3,000 years, as recorded by one of the first clinical pharmacologists, Emperor Shen-Nung in 2737 BC. During the late 1800s, the Indian Hemp Commission Report described cannabis as the most important drug in the Indian Materia Medica. During the 20th century, tincture of cannabis was included in the 1937 United States Pharmacopoeia and, in later years, in the United States National Formulary. The preparation was considered useful as an anti-inflammatory and analgesic agent for the relief of migraine headaches and prevention of seizures. In addition, it was used to treat psychiatric illness, including depression.[1] In subsequent years, it was replaced with therapies that were considered less toxic and more specific in their activity.

As Dr Anderson mentioned, we might have seen greater effects on IOP following cannabinoid treatment if we included patients with a condition other than end-stage glaucoma. I believe this is probably true. However, if one properly informs glaucoma patients about the proven benefits of conventional glaucoma therapy and contrasts this with the unproven potential benefits following marijuana derivatives, one cannot avoid endorsing the commercial agents much more enthusiastically. This is particularly true since all of the available cannabinoid derivatives have significant psychotropic effects. While these effects follow dose-response relationships that include drowsiness or feeling comfortably high, which can progress to depersonalization or even a panic reaction, external stimuli can abruptly shift the apparent dose-response curve so that the patient, while experiencing a happy high, can rapidly progress into a panic reaction without additional cannabinoid treatment. This is called endogenic potentiation.[2]

I agree with Dr Anderson that there is good evidence that the cannabinoids are capable of lowering IOP. This was initially described by Dr Robert Hepler during the 1970s.[3] I have included information about US government's grown marijuana that was available for patients in this study within the text of this paper. None of the enrolled subjects wanted to use inhaled marijuana because they did not like the idea of smoking with the associated pulmonary irritation and potential risk of lung cancer.

It is interesting to me that Dr Spaeth observed excessive toxicity and a lack of therapeutic effect in his attempts to use a topical form of marijuana in glaucoma

patients. I suspect Dr Spaeth's efforts were based in part on the initial reports by Dr John Merritt, who described topically applied marijuana in experimental animals. However, Dr Merritt was unable to duplicate these potentially beneficial effects on the IOP of humans.[4] Therefore, Dr Spaeth's observations are not too surprising. For the past 25 years, I have had the privilege of providing a 4-day ocular pharmacology and toxicology course at Stanford University during the summer months as part of a Basic Science Course for ophthalmologists. Each year, I have included a section on the cannabinoids and their potential use within ophthalmology. One of the graduates of this course who practices in Jamaica sent me a package insert for a commercially available *Cannabis sativa* solution marketed under the name of Canasol. This topically applied liquid is described as capable of lowering IOP as effectively as timolol without the side effects. However, there are no published studies that verify this ability.

I am certain that we are all as interested as Dr Cantor in the pharmacodynamics of cannabinoids. Dr Keith Green deserves a lot of credit for the time he has devoted to this study. His research describes many different potential mechanisms by which the cannabinoids can lower IOP.[5] However, I think that we need Dr Richard Brubaker, or someone with his experience studying human aqueous inflow and outflow, to conscientiously work out these effects. In conclusion, as I mentioned within the introduction to this paper, cannabinoid receptors have been identified within the human eye, but it remains to be elucidated how these receptors might be beneficially manipulated by exogenously applied or endogenously liberated cannabinoids or other lipid compounds and the mechanism underlying these activities.

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