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Is there a role for marijuana in the treatment of glaucoma?

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Abstract

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IS THERE A ROLE FOR MARIJUANA IN THE TREATMENT OF GLAUCOMA?

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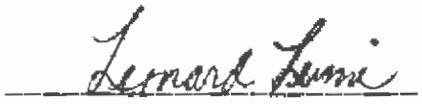

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BIOGRAPHICAL INFORMATION

Douglas Orton was born and raised in Southern California. He holds two degrees from the University of California at Irvine, a B.S. in Biological Sciences and a B.A. in Economics. He will graduate from the College of Optometry at Pacific University on May 20, 1990 (his 28th birthday). Upon graduation, Dr. Orton plans to practice in the coastal area of California.

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INTRODUCTION:

In 1971, Hepler and Frank reported that smoking marijuana significantly lowered the intraocular pressure (IOP) in nine of eleven healthy human subjects.[1] The fact that smoking marijuana decreased IOP was confirmed by subsequent experiments and reports soon surfaced suggesting marijuana use as a new treatment for glaucoma.[2,3] When scientific experiments are briefly summarized by the popular media, often times the information is incomplete and accepted uncritically. It is likely that this occurred with the studies done on cannabis and its derivatives in lowering IOP. An eyecare practitioner could easily be misinformed regarding the potential use of marijuana in treating glaucoma if the popular media and other secondary sources were his or her only reading. The purpose of this literature review is to critically summarize the research that has been done to determine the role, if any, cannabis derivatives may play in treating glaucoma. This is best accomplished by answering the following three questions:

1) How effective are marijuana and its derivatives in lowering IOP when administered by different clinically relevant methods?

2) What are the mechanisms of action of marijuana in lowering human IOP?

3) What are the possible ocular and systemic side effects that accompany the use of cannabis?

MATERIALS AND METHODS:

The reference literature for this review was obtained by running a MEDLINE File search via Paperchase™ using a MacIntosh Plus™ computer, a Supra™ 2400 baud modem, and the Red Ryder™ (9.4) communications software. Search terms used were, "cannabis," "marijuana," and "tetrahydrocannabinol," all combined with "glaucoma," using the Boolean "AND" operator. Pertinent articles were also obtained from the reference sections of four established textbooks on ocular pharmacology.[4,5,6,7] The MEDLINE citations were downloaded onto a floppy disk and the review was written using the Microsoft™ program WORD™ 4.0. The downloaded references file was opened as a separate window while creating this document. As references were cited in the text, they were "cut and pasted" from the reference window into the footnote window of the main text.

CLINICAL EFFECTIVENESS & SIDE EFFECTS:

It has been estimated that to control ocular hypertension by smoking marijuana, daily inhalation of four cigarettes would be required.[8] In this regard it is of interest that adverse pulmonary effects have been observed in subjects who smoked three marijuana cigarettes per week.[8] Further, laboratory analysis of marijuana smoke has shown a toxic effect at least equivalent to tobacco smoke on the genetic activity of cultured lung cells.[9] Finally, heavy marijuana smoking has also been shown to cause chronic bronchitis and metaplasia of the bronchial endothelium.[10] These considerations illustrate the risks of a treatment regimen consisting of marijuana *inhalation* for the typical glaucoma patient.

Thus, potential damage to the respiratory system that would probably accompany multiple marijuana cigarette smoking on a daily basis is one reason such a therapeutic regimen is unrealistic. However, it is not the only reason. Marijuana smoking is also accompanied by a variety of clinically undesirable physiological and psychological effects. Two well documented pharmacological effects of marijuana inhalation are a decrease in blood pressure[11,12] and tachycardia.[13,14] In a study in which "marijuana naive" adults with primary open angle glaucoma (POAG) smoked a single marijuana cigarette, a 14% decrease in mean blood pressure was observed which required a minimum period of sixty minutes to return to the pre-smoking level.[12] A study analyzing the pharmacologic effects of marijuana smoking in "healthy, experienced marijuana smokers" revealed a 60% mean heart rate acceleration approximately twenty

minutes after smoking a single marijuana cigarette, with the pulse rate remaining above the pre-smoking level for an average of ninety minutes.[14]

In an experiment in which glaucoma patients orally ingested the minimal dose of THC required to significantly lower their IOP's, the trials had to be prematurely discontinued due to "severe psychologic and cardiac complications."[15] These complications were described as "acute panic reactions, varying states of anxiety concerning tachycardia and palpitations, depersonalization reactions, and paranoic tendencies."[15] These side effects would obviously discourage patient compliance with any drug therapy, especially in chronic disease conditions such as glaucoma. The psychological effects of daily marijuana smoking or THC ingestion would also place extensive restrictions on patient's normal daily activities, such as driving a car.[8]

Recognizing the IOP lowering effects of smoking marijuana and considering its undesirable side effects, research efforts oriented toward identifying which constituent(s) of marijuana were responsible for the observed IOP reduction. The ultimate goal of the research was a preparation containing the IOP lowering component(s) of marijuana but lacking the side effects observed from smoking marijuana.

In 1964, delta-9-tetrahydrocannabinol (THC) was identified as the major psychoactive component in marijuana.[16] After the IOP lowering capabilities of marijuana were confirmed, experimentation proceeded to determine the IOP lowering effects of THC in human and animal subjects. Experiments were also performed to determine

the IOP lowering abilities of cannabinoids such as delta-8-THC, 11-OH-delta-9-THC and related synthetic analogs. Rabbits were the subjects in the majority of these investigations.

ORAL AND INTRAVENOUS THC:

Studies in which encapsulated synthetic THC has been orally ingested in human subjects have shown IOP decreases similar in magnitude to that observed when marijuana is smoked.[15,17] Intravenous THC administration in humans has also resulted in substantial IOP reductions.[18] Systemic hypotension, tachycardia, and the psychological side effects that accompany marijuana smoking were also observed when THC was administered orally or intravenously.[15,17,18]

TOPICAL THC:

The side effects which accompany marijuana inhalation, and oral and intravenous THC administration were not found when THC was administered as a topical ophthalmic preparation. Green conducted an experiment in which THC was applied topically to rabbit eyes six times daily for a period of thirty days.[19] Blood and urine samples from each animal were analyzed before the drug administration began and again on day twenty nine. The subjects' general health along with specific ocular parameters were observed regularly. On day thirty, all the rabbits were sacrificed and their ocular tissues were examined histologically. The authors concluded that, aside from eyelid irritation caused by the vehicle, there were "no important adverse effects of clinical significance caused by the concentrations of THC" used in the study.[19]

A double blind, randomized, controlled study using human volunteers produced similar results with respect to ocular irritation.[20] THC was administered topically to each subject four times daily for a one week period. Of the initial twenty eight paid volunteers, five had to discontinue participation due to a burning sensation and/or lid swelling. However, those five subjects, four were in the control group, receiving the light mineral oil vehicle alone. No other ocular or systemic side effects were observed with any of the subjects in the treated group.[20]

Animal studies gave encouraging results with respect to the IOP lowering abilities of THC and other cannabis derivatives. Green et al. reported a 25% mean IOP reduction in rabbits following intravenous administration of THC.[21] Similar results were also reported by ElSohly et al. in a separate experiment.[22] Green has also reported extremely high reductions in IOP when a high molecular weight hydrophillic fraction of cannabis was intravenously administered to rabbits.[23] IOP reductions have also been reported in rabbits when various doses of delta-8-THC, 11-OH-delta-8-THC, and cannabinol have been intravenously administered.[22]

In contrast, studies in which THC and other related compounds were administered *topically* as ophthalmic preparations to rabbits have produced conflicting reports. On the one hand, Green has repeatedly reported that topical THC significantly reduces IOP in rabbits.[24,25] On the other hand, ElSohly has reported no significant IOP lowering effects from topical THC to rabbit eyes.[22,26] When the studies by ElSohly are compared to the studies by Green, three major differences in experimental design become apparent. The first dif-

ference is in the control groups used. ElSohly used the same group as controls throughout the experiment, whereas Green used the same rabbits as test animals one day and control animals the next. The neurological condition of some of the rabbits used in the two studies also differed. Normal adult rabbits were used in the two experiments ElSohly performed.[22,26] Green used normal adult rabbits and adult rabbits that had been subjected to unilateral superior cervical ganglionectomy.[24,25] Green reported the observed IOP reductions in the eyes contralateral to the lesion as occurring in "normal" rabbit eyes. There were also differences in the number of subjects used in the studies by ElSohly and Green. ElSohly consistently used eight rabbits as subjects and eight rabbits as controls.[22,26] In one study, Green reports mean percentage IOP reduction values as being derived from, "at least 6 eyes of 6 animals for each drug concentration."[24] The experimental design of ElSohly is superior in determining the IOP lowering ability of topical THC because negative controls were used and a greater number of *normal* rabbits were used. In light of this negative evidence, Green's results do not appear convincing.

Green has also reported IOP reductions of 30% with topical administration of synthetic THC analogs in rabbit eyes.[21] IOP decreases of up to 25% have also been reported by ElSohly following topical administration of other synthetic marijuana derivatives.[26]

A widely cited Jamaican study reported that a water soluble extract of whole cannabis applied as a topical ophthalmic solution reduced mean IOP's in 23 glaucoma patients a minimum of 32.5% with no adverse side effects.[27] Few who quote this study, however, note

that the frequency of administration was not given. Also, the experimental protocol did not utilize a control group, and the solvent used to prepare this ophthalmic solution was not mentioned, nor used alone as a control. This alleged topically administered water soluble cannabis derivative has not been identified, despite diligent attempts by Green et al.[23,28] It is puzzling why this study was so frequently accepted in the literature, when the experimental design was so blatantly poor.

The side effects found to accompany marijuana smoking, and oral and intravenous THC administration indicated the need for a drug delivery method that bypassed the central nervous system. This consideration, along with the IOP reductions reported in rabbits with topical cannabinoid drops, inevitably led to topical THC trials with human subjects. Three controlled studies have been performed measuring IOP following topical administration of varying concentrations of THC in a light mineral oil vehicle. A previous report by Green determined light mineral oil to be the vehicle of choice for topical ocular application.[29] Green found that light mineral oil showed no corneal toxicity and delivered the largest quantity of THC across the rabbit cornea, when compared to heavy mineral oil, sesame oil, and a glycol oleate.[29]

One study using 0.05% and 0.10% topical THC solutions administered to six subjects with POAG found no significant effect on IOP, heart rate or blood pressure resulting from the drug administration.[30] Another study in which normal subjects were administered a single drop of 1% topical THC (10-20 times the concentration of the previous study), likewise reported no effect on IOP.[31] In yet a third

study, involving 23 normal subjects receiving 1% topical THC four times daily for one week, no significant effect on IOP, blood pressure, pulse rate or respiratory rate was found.[20] Thus, present evidence indicates that topical THC is ineffective in lowering IOP in humans.

PHARMACOLOGY:

Experimental results from both human and animal studies have led to a great deal of uncertainty regarding the mechanism of action of marijuana and/or THC in lowering IOP in man. In a 1980 article, Green and Roth[32] hypothesized that the IOP fall observed in rabbits after intravenous THC administration is "primarily" due to an increased facility of aqueous outflow. This hypothesis was based on a study they performed in 1973 on anesthetized rabbits and *in vitro* rabbit uveal tissues.[33] In the same article, the authors note that other animal studies have also shown a decrease in aqueous formation, a central nervous system effect, and alpha and beta adrenergic effects in the eye following THC administration.[32]

In a 1982 study by Green et al.[34], THC was intravenously administered to rabbits and rhesus monkeys. The study found that intravenous THC lowered rabbit IOP's but had no IOP lowering effects in rhesus monkeys. From these results Green et al. concluded that, "species differences exist in the ocular responses to cannabinoids and that extrapolation of rabbit data to primate must be experimentally verified."[34] This statement illustrates the substantial need for further experimentation to determine the site(s) and mechanism(s) of action by which THC lowers human IOP. Extrapolating from rabbit studies is insufficient.

Crawford and Merritt have suggested a centrally mediated mechanism of action to explain the IOP reductions seen following marijuana inhalation. Their hypothesis is based on their experimental observations in studies using human subjects. Heart rate, IOP, and blood pressure were all measured at regular intervals following

the smoking of a single marijuana cigarette by a group of POAG patients. After the measured parameters had returned to pre-smoking levels, the time courses of each variable were plotted and compared. It was found that the changes in mean arterial pressure paralleled the changes in IOP.[12] The author's concluded from this observation that the decrease in systemic blood pressure leads to decreased capillary pressure at the ciliary body which results in a decrease in aqueous humor production.[12] In support of their hypothesis, the author's cite a study in which IOP was measured in patients following oral administration of either propanolol or atenolol.[35] This study also found that the maximal IOP reductions occurred simultaneously with the maximal systolic blood pressure reductions.[35]

It is well accepted that the ultrafiltration component of aqueous production is dependent on the pressure gradient at the capillaries of the ciliary body.[36] Thus, it logically follows that a decrease in blood pressure at the ciliary processes would result in a decrease in the ultrafiltration component of aqueous production. If the Crawford/Merritt hypothesis regarding the mechanism by which marijuana lowers IOP is correct, then there is a significant limit to the amount of IOP lowering marijuana could induce. There is also secretory component to aqueous production that is not influenced by capillary pressure at the ciliary body.[36]

The aforementioned centrally mediated mechanism of action proposed by Crawford and Merritt probably accounts for at least a partial amount of the observed IOP reduction accompanying marijuana use. It would be premature however to conclude from the

available evidence how much of the IOP reduction is due to the systemic hypotension induced by THC administration.

Benowitz et al. have reported that pretreatment with both atropine and propranolol is required to completely inhibit the cardiovascular effects of intravenous THC.[37] This indicates that THC acts on both divisions of the autonomic nervous system. The eye is innervated by both divisions of the autonomic nervous system.[38] Drugs presently prescribed to lower IOP's in glaucoma patients include a parasympathomimetic (Pilocarpine), a sympathomimetic (Epinephrine) and its pro-drug (Dipivefrin), and a group of Beta adrenergic antagonists (Timolol, Betaxolol, and Levobunolol).[38] These drugs are all administered as ophthalmic drops and exert their effects via a local mechanism of action on specific ocular tissues. The observation that THC exhibits autonomic activity on the cardiovascular system makes it probable that such activity occurs in the eye as well.

DISCUSSION:

I believe that (a) the potential pulmonary health hazards, (b) the documented clinically unacceptable physiological effects, and (c) the unpredictable impairment of mental functioning that accompany marijuana smoking, preclude such therapy for the routine treatment of glaucoma. The three aforementioned considerations continually present themselves in the literature and are the apparent reasons that marijuana inhalation has been disregarded in the scientific literature as a means of stabilizing IOP in typical glaucoma patients.

A substantial amount of further research is required to understand the means by which marijuana lowers IOP in humans. The presence of a local effect on ocular structures must first be clearly demonstrated and at least partially understood before a topical glaucoma medication can be developed from cannabis. The currently accepted centrally mediated IOP reduction secondary to systemic hypotension argues against the development of a locally acting glaucoma medication from cannabis.

Nineteen years ago, Hepler and Frank reported that marijuana smoking lowered the IOP in human subjects. The failure thus far to develop a preparation of cannabis that is capable of lowering IOP with minimal side effects, I feel, diminishes the possibility of a future role for marijuana in routine glaucoma treatment. Further, the recent development of effective, topical preparations such as timolol, betaxolol and levobunolol, that possess minimal side effects in most people and have been widely accepted by the medical community,[39] decrease the need for a cannabis preparation. In addition, it has

been noted that since cannabinoids are naturally occurring substances, they are unpatentable[40] and thus unattractive to pharmaceutical companies wishing a return on the large research and development expenses that would be required to develop F.D.A. approved medicinal derivatives from marijuana.

A final point is that, although marijuana has been shown to lower IOP, there have not been any studies determining whether or not visual function is preserved following marijuana induced IOP reductions.

CONCLUSIONS:

1) Marijuana smoking, oral, and intravenous THC administration all exhibit IOP lowering effects in rabbits and human beings.

2) THC prepared as a topical ophthalmic solution in mineral oil does not lower IOP in normal rabbits or in human beings.

3) A cannabis preparation that exhibits IOP lowering abilities and is free of clinically undesirable side effects has not been developed.

4) The site(s) and mechanism(s) of pharmacological action of THC in lowering IOP is not presently known.

5) The development of Timolol, Betaxolol, and Levobunolol in the 1980's has provided eyecare practitioners with additional safe, effective, topical glaucoma medications, and substantially reduced the need for a cannabis preparation.

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