ANTIGLAUCOMA EFFECTS OF TOPICALLY AND ORALLY ADMINISTERED CANNABINOIDS

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I. INTRODUCTION

The studies by Hepler and Frank in 1971 (1), led to the discovery of marijuana as an agent capable of lowering intraocular pressure (IOP) in humans and thereby indicating a therapeutic use for this material in the treatment of glaucoma.

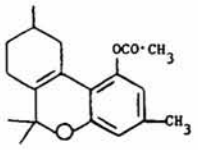
Although, delta-9-tetrahydrocannabinol (THC) is clearly effective at lowering IOP in humans when smoked (1), given intravenously (2), or orally (3), results with topical formulations have been disappointing (4). This is surprising in view of the reported significant lowering in IOP in experimental animals following topical administration of THC (5,6).

Similarly, pirnabine (Fig. 1) was studied by us in 1977 and shown to be ineffective when administered topically to humans in spite of reported IOP lowering in animals (7).

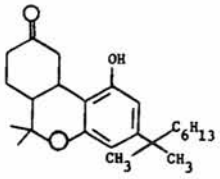
Using the normotensive rabbit as a model we have reinvestigated the effects of topically applied drugs on the IOP. The data are summarized in Table I. The results of these studies failed to confirm the previously reported animal data for cannabinoids, but seemed to parallel the results in human studies with THC and pirnabine. Using the oral route of administration, THC, nabilone and nabitan all caused statistically significant lowering of IOP in normotensive rabbits.

Nabitan was also as effective in lowering IOP of human ocular hypertensives (8), when administered orally, but suffered from cardiovascular side effects at effective doses.

Naboctate was developed at SISA Incorporated as an oral antiglaucoma agent. It will lower IOP when administered orally to the normotensive rabbit (9) or to normal human volunteers (10). The incidence of cardiovascular side effects is markedly reduced with this compound and doses which signifi-



PIRNABINE



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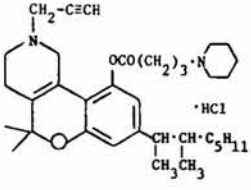

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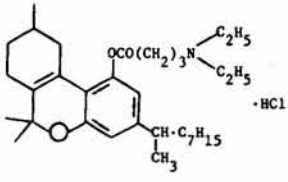

NABOCTATE

FIGURE 1. Structures of cannabinoids discussed in text.

TABLE I. Summary of effects of topically administered drugs on the intra-ocular pressure of the normotensive rabbit

Compound	Vehicle	Effect on IOP
Epinephrine	Water	Dose relatedfall: long duration
Pilocarpine	Water	Small transient fall
Timolol	Water	Small transient fall
THC	Lt. min. oil	No effect
Pirnabine	Lt. min. oil	No effect
Nabilone	PEG. 200	No effect
Nabitan	Water	Weak, erratic effect: irritation

cantly reduce IOP in normal human volunteers were below the lowest dose causing subjective CNS effects.

In the normotensive rabbit, naboctate administered topically gave a weak ocular hypotensive response (Fig. 2).

By temporarily elevating the IOP of the rabbit using the water loading procedure described by Vareilles et al. (11), we have been able to demonstrate an ocular hypotensive action to topically administered naboctate. Table II is a flow diagram of the protocol used for these studies.

Figures 3, 4, 5 and 6 show the results obtained with aqueous naboctate at 0.2%, 0.5% and 1% and with timolol at 0.25% respectively. In this model naboctate shows a dose related response on the intra-ocular pressure. The results with timolol confirm the data generated by Vareilles et al. (11). The choice of an aqueous vehicle for naboctate was important since even at concentrations of up to and including 2% in light mineral oil naboctate was ineffective in lowering IOP in this model. Nabilone was also ineffective when administered topically in light mineral oil, whereas THC did produce a weak ocular hypotensive response (Fig. 7).

These studies demonstrate the importance of the vehicle for delivering drug. Studies with naboctate in the normal

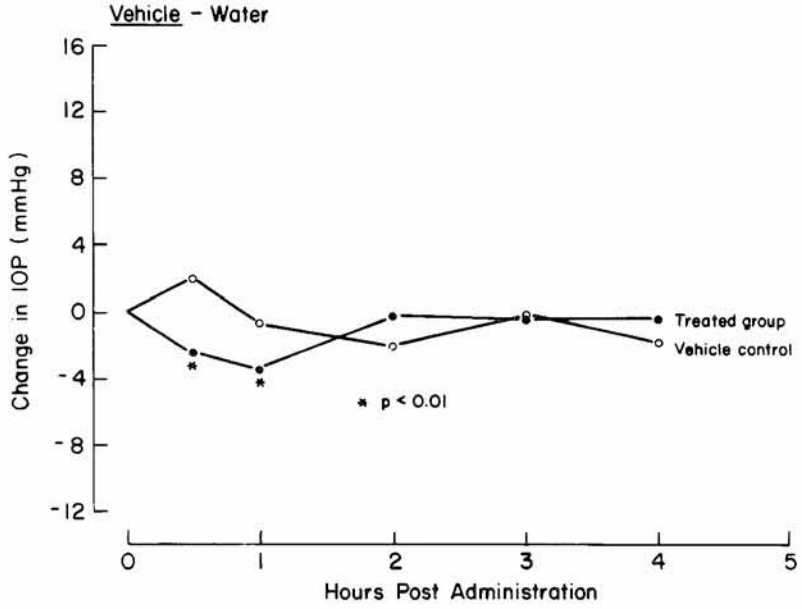

FIGURE 2. Effect of naboctate (0.8% topically) on the IOP of normal rabbits. Vehicle: water. ● = Treated group; o = vehicle control; *p < 0.01.

TABLE II. Protocol for Studying Topical Drugs in the Temporarily Ocular Hypertensive Rabbit

Day	Group I (N = 4)	Group II (N = 4)
1	a. 2 control IOP readings b. 100 ml/kg water by stomach tube c. 0.05 ml test drug solution to both eyes d. determine IOP at 1/3, 1, 2, 3 & 4 hours	a. 2 control IOP readings b. 100 ml/kg water by stomach tube c. 0.05 ml control vehicle to both eyes d. determine IOP at 1/3, 1, 2, 3 & 4 hours
2,3	No studies	No studies
4	a. Same as day 1 b. Same as day 1 c. 0.05 ml control vehicle to both eyes d. Same as day 1	a. Same as day 1 b. Same as day 1 c. 0.05 ml test drug solution to both eyes d. Same as day 1

rabbit (without water loading) demonstrated that an oral dose of 20 mg/Kg naboctate was an effective ocular hypotensive when the vehicle was water, less so when sesame seed oil was used and was inactive when light mineral oil was used as the vehicle (see Figures 8, 9 and 10). THC administered orally in light mineral oil was shown to be active (Fig. 11).

II. Conclusions

Cannabinoid drugs clearly lower intra-ocular pressure in humans. Whether this is best achieved by oral administration of drugs or by topical administration, is still open to question. Topically applied cannabinoids have so far been disappointing, probably due to the use of non-aqueous formulations. Water soluble compounds such as naboctate show promise of being useful topically but stable formulations of these materials have to be developed.

While there is little doubt that cannabinoids will be effective orally, there are other problems to be faced when using this route of administration. Although side effects with naboctate do not appear to be a problem, at the proposed dosages, there is only a small margin between these and doses

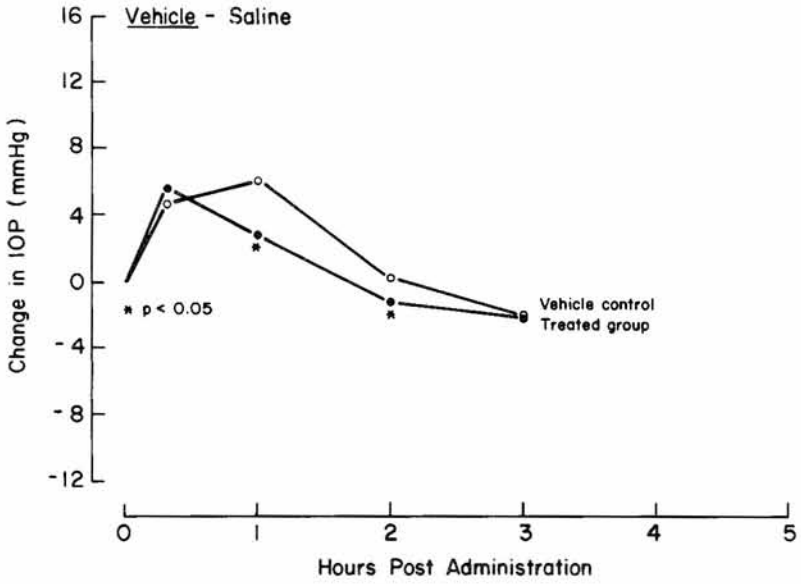

FIGURE 3. Effect of naboctate (0.2% topically) on the IOP of water loaded rabbits. Vehicle: saline. ● = Treated group; o = vehicle control; *p < 0.05.

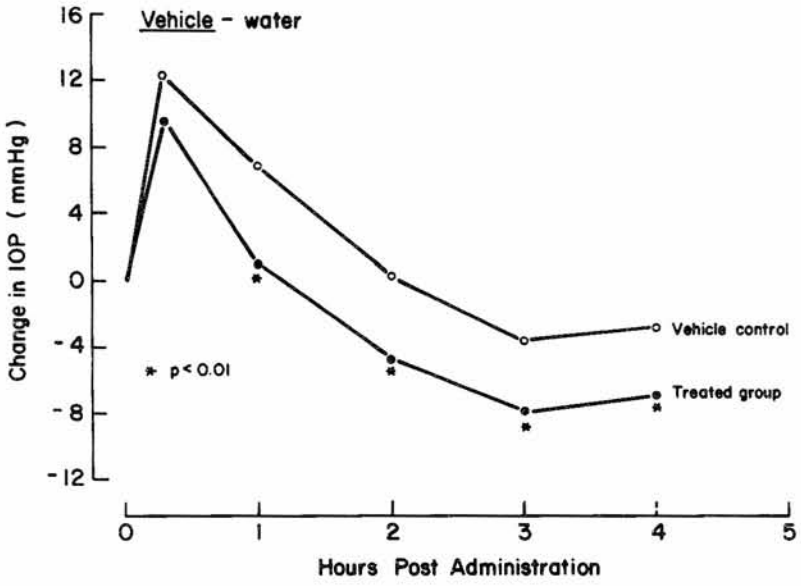

FIGURE 4. Effect of naboctate (0.5% topically) on the IOP of water loaded rabbits. Vehicle: water. ● = Treated group, o = vehicle control; *p < 0.01.

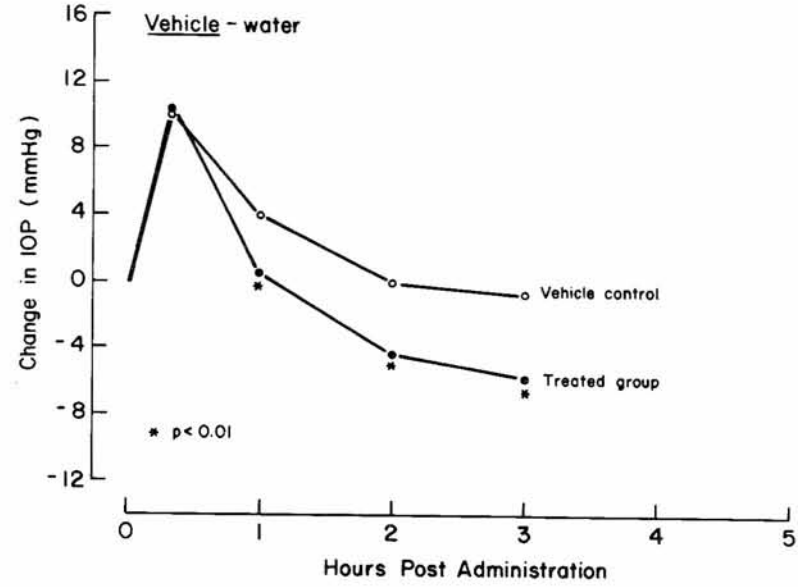

FIGURE 5. Effect of naboctate (1.0% topically) on the IOP of water loaded rabbits. Vehicle: water. ● = Treated group, o = vehicle control; *p < 0.01.

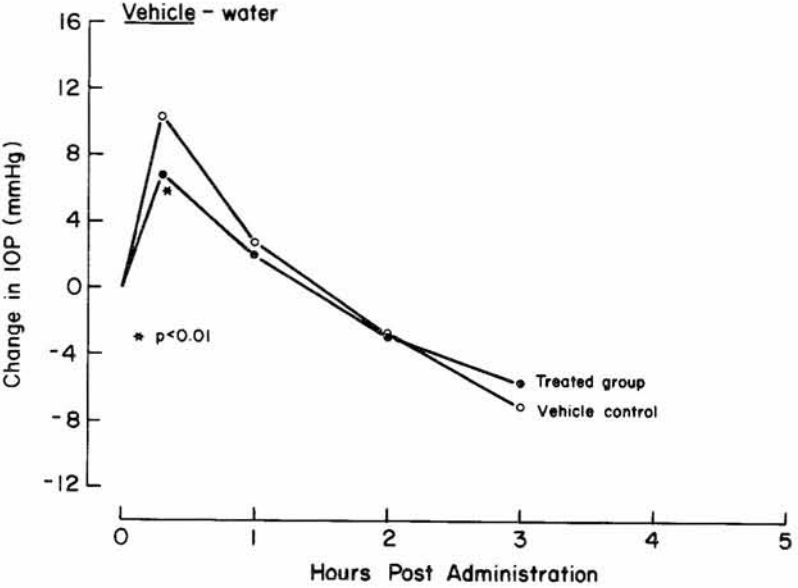

FIGURE 6. Effect of timoptic (0.25% topically) on the IOP of water loaded rabbits. Vehicle: water. ● = Treated group; o = vehicle control; *p < 0.01.

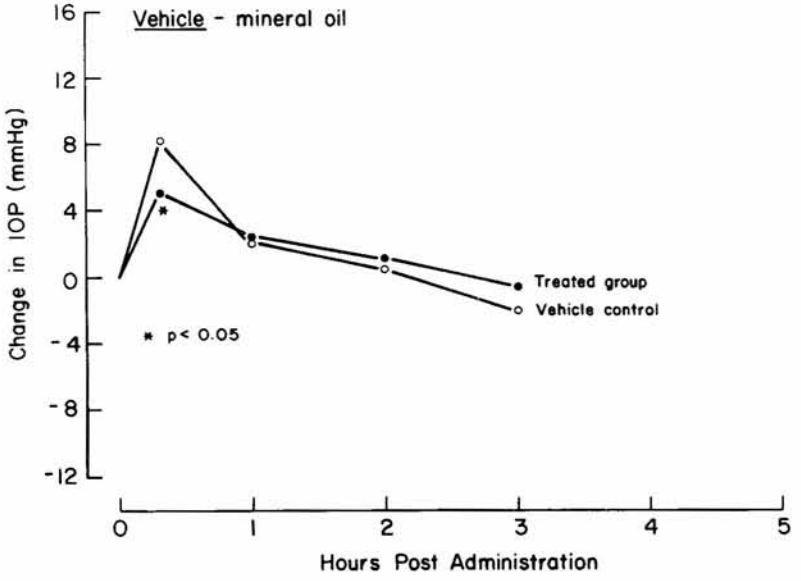

FIGURE 7. Effect of THC (1.0% topically) on the IOP of water loaded rabbits. Vehicle: mineral oil. ● = Treated group; o = vehicle control; *p < 0.05.

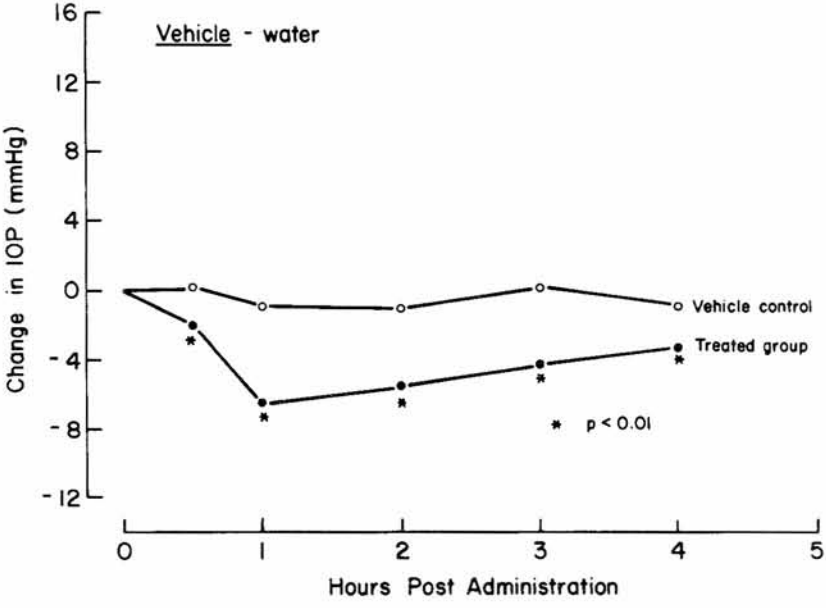

FIGURE 8. Effect of naboctate hydrochloride (20 mg/kg p.o.) on the IOP of normal rabbits. Vehicle: water. ● = Treated group; o = vehicle control; *p < 0.01.

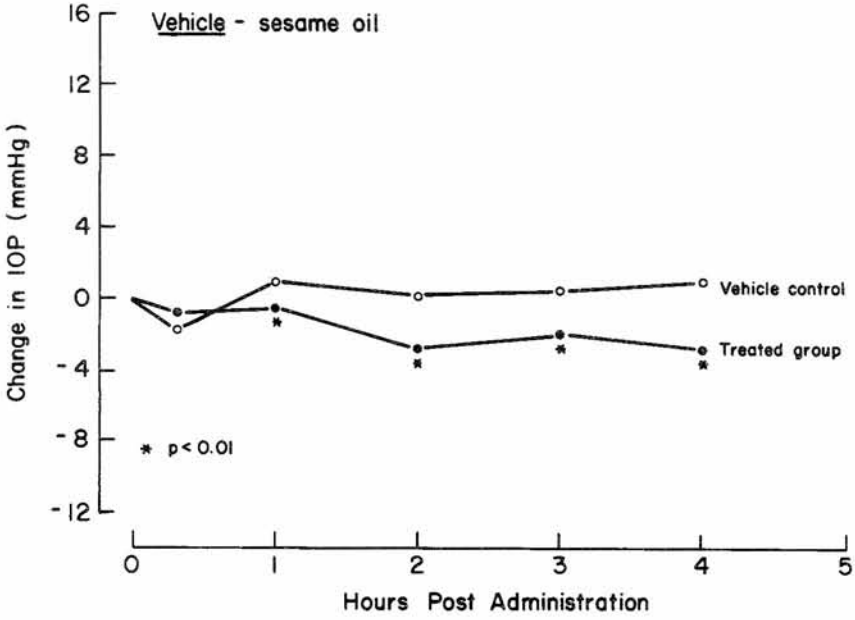

FIGURE 9. Effect of naboctate free base (20 mg/kg p.o.) on the IOP of normal rabbits. Vehicle: sesame oil. ● = Treated group; o = vehicle control; *p < 0.01.

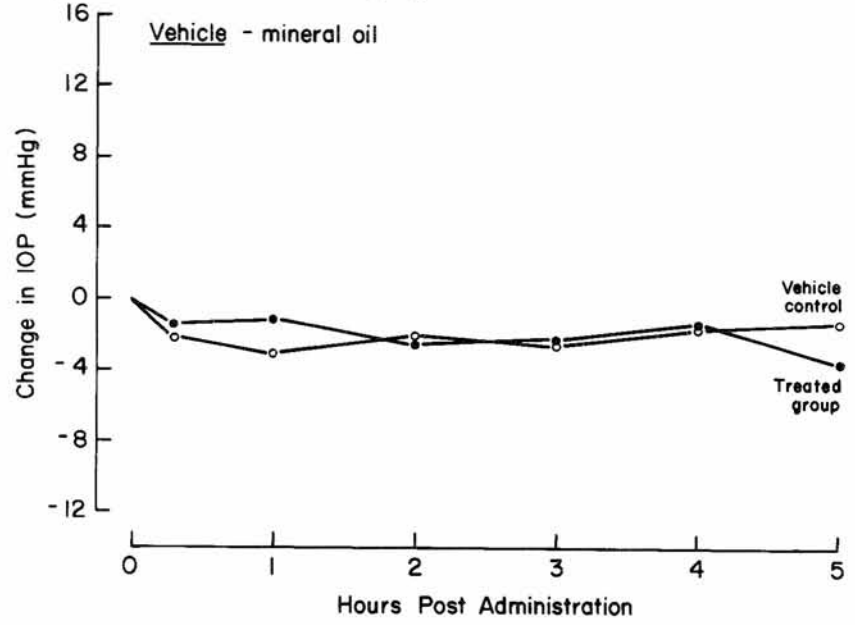

FIGURE 10. Effect of naboctate free base (20 mg/kg p.o.) on the IOP of normal rabbits. Vehicle: mineral oil. ● = Treated group; o = vehicle control.

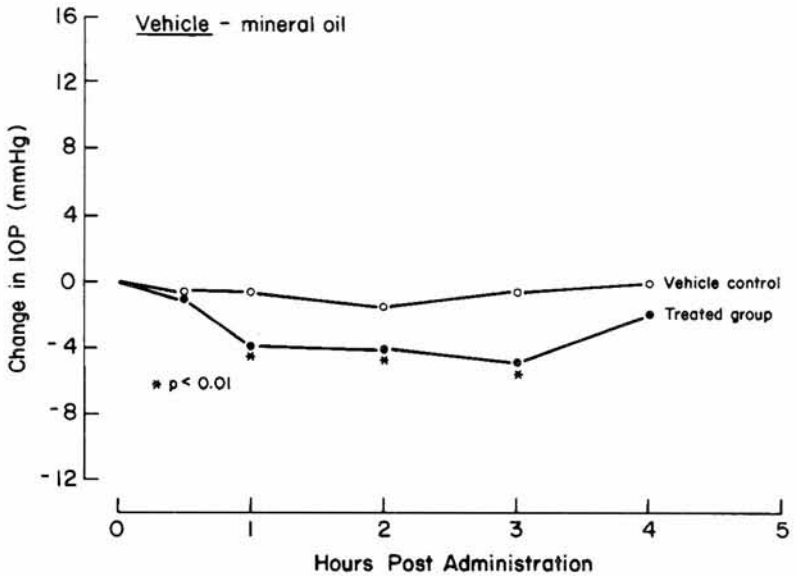

FIGURE 11. Effect of THC (20 mg/kg p.o.) on the IOP of normal rabbits. Vehicle: mineral oil. ● = Treated group; o = vehicle control; *p < 0.01.

producing side effects. Furthermore, an oral formulation is more likely to be diverted for abuse.

There are not yet adequate data available to allow one to speculate on the place that the cannabinoids will occupy in the therapy of glaucoma. Primarily, subjects refractory to other drugs, particularly timolol, would be candidates. A lot more work in humans must be carried out before this class of compound finds a niche in glaucoma therapy.

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