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Cannabinoid Penetration and Chronic Effects in the Eye

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The penetration of topically applied ^{14}C-labelled Δ^9-tetrahydrocannabinol (THC) from various vehicles into the eye has been measured, and a low viscosity light mineral oil proved to be most efficient. Further delineation of oils was made on the basis of the physiological intraocular pressure decrease in response to topical THC and the least viscous oil (11 cP) proved most efficacious. Both 9- and 60-day studies were made with both an oil soluble and water soluble cannabinoid related to THC. Drops were applied topically, $2 \times 50\,\mu$l per day, and the intraocular pressure response noted daily in the 9-day study and approximately once weekly in the 60-day study. The intraocular pressure always fell by about 20% at the dose levels employed here in response to the drugs and no tolerance was noted. The water soluble derivative produced a greater intraocular pressure reduction in ganglionectomized eyes.

Key words: tetrahydrocannabinol; vehicles; intraocular penetration; cannabinoids; chronic studies; rabbit; intraocular pressure; drug tolerance; ganglionectomy.

1. Introduction

The efficacy of Δ^9-tetrahydrocannabinol (Δ^9-THC) in reducing IOP is undisputed (Green, 1975) whether delivered, in low doses, intravenously or by smoking. For potential clinical use, however, a topical drop form of one of the cannabinoids or another related compound is more desirable since unacceptable psychotropic action could be avoided and since it is readily self-administered.

One recent study has examined the effect of orally administered cannabinoid derivatives on the intraocular pressure (IOP) in dogs for up to 7 days (Thompson and Yang, 1976), but there is a paucity of reports on chronic administration of these compounds with regard to their ocular effects. Preclinical studies should, therefore, establish whether the cannabinoids enter the eye when delivered in drop form and if so, whether chronic drop treatment remains efficacious in reducing the intraocular pressure.

Two major problems include defining the most desirable drug and the vehicle in which it is to be administered. The present paper reports studies on (a) the ocular penetration of Δ^9-THC from different vehicles and (b) the effects of daily administration of cannabinoids versus the newer benzopyranopyridines (Pars and Razdan, 1976) over both 9 and 60-day periods.

2. Materials and Methods

Adult albino rabbits, 2–4 kg, of either sex were used.

Ocular penetration of Δ^9-THC

Δ^9-THC was dissolved to a final concentration of 0·1% in four vehicles; paraffin oil, LMO (Fisher Scientific Co., laboratory grade, white, light, domestic); mineral oil, HMO (Squibb, mineral oil, intestinal lubricant); sesame oil, SO (Hain Pure Food Co., Inc., Los Angeles, Calif.); or a mixture of 90% normal saline solution (0·9% NaCl) and 10% Tween-80 (polyoxyethylene (20) sorbitan monooleate, Fisher Scientific Co.). The solutions contained 20% of the Δ^9-THC in ^{14}C-labelled form (68 μCi/mg, supplied by the National Institute on Drug Abuse). Each eye of an animal received a different

vehicle in order to reduce individual animal differences. All preparations were added as one 50 μl drop to the cornea at the 12 o'clock position, and at various time intervals the following procedure was performed. The proptosed eye was washed with at least 2 ml of saline, to remove excess Δ^9-THC, and an anterior chamber paracentesis performed with withdrawal of approximately 150 μl of aqueous humor. After receiving an overdose of sodium pentobarbital the cornea was removed, followed by the lens and iris. The tissues and 100 μl of aqueous humor were separately digested in a tissue solubilizer (Protosol, New England Nuclear Corp., Boston, Mass.) at 50°C for 24 hr and were then placed into 10 ml of scintillation fluor (Liquifluor, New England Nuclear Corp., Boston, Mass.) for determination of radioactivity in a Packard Tri-Carb scintillation counter. The counting efficiency for all samples was 72% based on a quenching curve.

Comparison of vehicles

Based upon the ocular penetration data four oils (three mineral oils and a glycol oleate) of varying viscosity, were used as vehicles to prepare a 0·1% solution of Δ^9-THC. These were tested in conscious rabbits to compare their effectiveness of presentation of the drug as determined by the reduction of intraocular pressure. The oils containing Δ^9-THC were prepared by Dr J. Olsen and were assessed for their relative efficacy in reducing intraocular pressure (IOP) in a single blind manner such that the oil used was unknown to those who measured IOP. The oils were supplied in coded sterile vials which delivered a drop of 25 μl volume.

The IOP was determined on the topically anesthetized cornea using an Alcon Pneumatonograph, calibrated for rabbit eyes. One drop of proparacaine hydrochloride was placed on the cornea and 5–10 sec later washed off with an excess of 0·9% sodium chloride solution so that local anesthesia could be induced without affecting the corneal epithelial integrity. Earlier work (Green, Kim and Bowman, 1976; Green and Kim, 1976a, b) has shown that Δ^9-THC causes a substantial IOP fall only in eyes with an intact adrenergic nervous system, and that superior cervical ganglionectomy reduces this effect by 60% (Green and Kim, 1976b). It was of interest, therefore, to compare the vehicle efficacy in both normal and ganglionectomized eyes, since one of the vehicles could be responsible for enhancing the penetration of Δ^9-THC into the eye more than the others and concurrently eliciting a greater direct effect in the ganglionectomized eye. Unilateral superior cervical ganglionectomies were performed under urethane anesthesia and the animals were tested for supersensitivity 10 days later with 0·1% norepinephrine solution applied topically to the eye. The normal eye did not respond but the ganglionectomized eye developed a full mydriasis. At least four additional days were allowed for exogenous norepinephrine to dissipate from the eye before experimental use. The Δ^9-THC was applied in the oils (2×25 μl drops 5 min apart) to either the normal right or ganglionectomized left eye. Two drops were applied since in all previous studies (Green and Bowman, 1976; Green, Kim and Bowman, 1976) a 50 μl drop had been used and this enabled a direct comparison both with previous drugs as well as the presently employed vehicles. The 5 min interval was suggested from other work to be advantageous when delivering two drops to the eye (Chrai et al., 1974).

Nine-day chronic administration involving two new cannabinoid analogs, SP-1 and SP-106

IOP was determined at 30-min intervals for 7½ hr each day using an Alcon Pneumotonograph. The initial (0 min) and second (30 min) IOP determinations each day rarely varied by more than 1 mmHg and were therefore taken as the pre-drug value. The drug, in one 50 μl drop, was applied twice each day either to the right or left eyes of unilaterally (left) superior cervical ganglionectomized rabbits immediately after the 30 min IOP determination and again after the 270 min IOP determination. Half of the animals received a drop in the right eye and the remainder received a drop in the left eye. The purpose of this study

with new derivatives was to examine the efficacy of each drug in lowering IOP in the normal and ganglionectomized eye and to determine any contralateral effects.

The cannabinoid analogs, SP-1 and SP-106, were supplied by SISA of Cambridge. SP-1 is an oil soluble nitrogen analog of Δ^9-THC, modified to have the form of a white powder (Pars et al., 1976), and SP-106 is a water soluble form of SP-1 (Razdan, et al., 1976). SP-1 was solubilized in mineral oil (Fisher Scientific Co.) and SP-106 was dissolved in 1% hydroxypropyl methylcellulose containing 0·1% benzalkonium chloride (Ultratears, Alcon Labs, Fort Worth, Texas). A 0·1% preparation of either drug was used since preliminary experiments indicated that 0·01% of each drug caused only a small (8–10%) IOP reduction. Only one drug was used in one animal.

Sixty-day chronic administration

The same animals that were used in the 9-day administration study were continued in longer-term experiments of 9 weeks during which they received 2 drops daily. IOP readings were made at approximately weekly intervals, every hour over a $7\frac{1}{2}$-hr period during the test-day following the initial 0 and 30 min pre-drug determinations. The same drug application and IOP determination regimen was followed as in the 9-day chronic administration study.

Concurrently, other animals received 3 drops per day of the light mineral oil for 4 weeks, to assess whether vehicle alone caused any irritation.

3. Results

Ocular penetration of Δ^9-THC

The topical application of a single drop of 0·1% Δ^9-THC in LMO gave the highest levels of labelled Δ^9-THC in the aqueous humor, iris and cornea, with HMO and SO being lower and the saline/Tween 80 solution providing the least penetration (see Fig. 1). The least viscous oil, therefore, gave the best penetration. The lens content of THC is close to those of aqueous humor at 1 hr but falls below the aqueous values at succeeding times. Fifty μg of Δ^9-THC were applied to the eye in the 50-μl drop, thus only about one millionth of the applied THC is found after 6 hr in the aqueous humor. The cornea contained about ten times more than that of the iris and aqueous humor (on a total tissue wet weight basis), irrespective of the vehicle, so that the cornea seems to act as a reservoir for intraocular Δ^9-THC. In four rabbits, labelled Δ^9-THC was applied to one eye only, and after 1 hr the animals were killed and aqueous humor, iris, cornea and blood samples were taken. The two eyes were compared in terms of the percentage of radioactivity in the eye not receiving the drop versus the eye receiving the drop and the results are as follows: cornea 0·03:1; aqueous humor 0·18:1; iris 0·68:1.

Comparison of vehicle

The IOP reduction caused by Δ^9-THC in four different oils is shown in Table I. The primary difference between the oils is their viscosity, and the least viscous provided the most effective reduction of IOP by Δ^9-THC. As can be seen in Table I the left, or ganglionectomized, eye shows an IOP fall which is about 30 or 40% of that seen in the normal eye. This phenomenon occurs despite placement of the drop in the ganglionectomized eye.

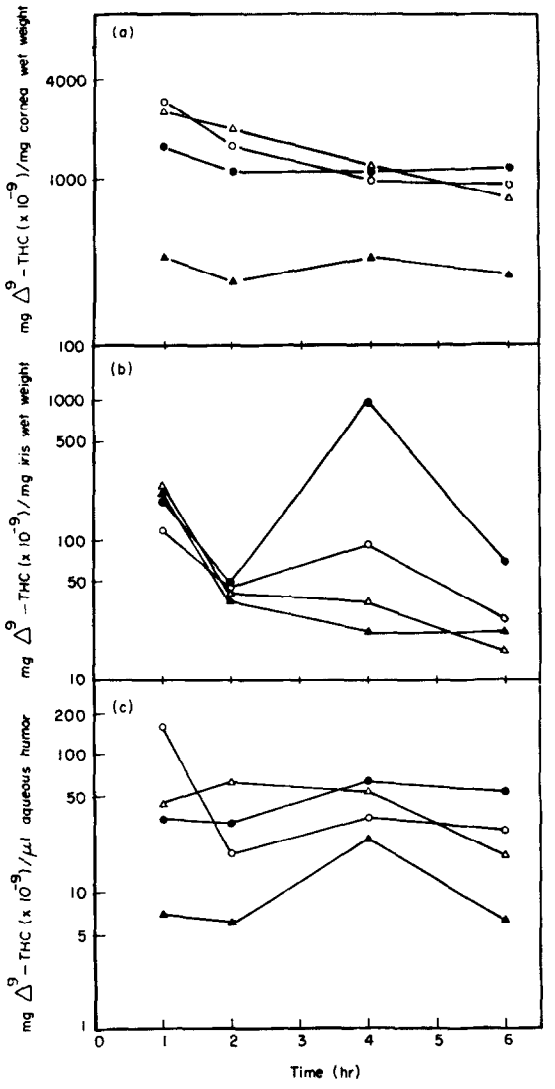

FIG. 1. Concentration of ^{14}C-labeled Δ^9-THC in (a) cornea, (b) aqueous humor and (c) iris of rabbit eye from four vehicles. ●, light mineral oil (LMO); ○, heavy mineral oil (HMO); ▲, sesame oil (SO) and △, saline/10% Tween-80.

Chronic administration

Both 0·1% SP-1 and 0·1% SP-106 cause a fall in IOP over a 9-day period when given topically on a twice-daily regimen (Table II) although there are small differences between the pressure fall on successive days. There is no evidence of tolerance, however, since the IOP always falls. No significant effect was observed on pupil diameter which was also measured daily. The trend was to a more miotic pupil in both normal and ganglionectomized eyes, although no statistical difference could be demonstrated. The maximum IOP fall in a normal eye caused by 0·1% SP-1 was about 20% at 120 min and for SP-106 was about 17%. By comparison, a concentration of 0·01% caused a maximum fall of 11·7% at 240 min for SP-106 and 9·5% at 180 min for SP-1 (not shown here). Four hr after the instillation of the first drop the IOP rises but the

administration of the second drop causes the IOP to fall once again to values as low as those seen during the first drop.

Data obtained at approximately weekly intervals on animals which received a 50-μl drop of 0·1% SP-1 or 0·1% SP-106 twice daily for 60 days showed the same IOP fall in normal and ganglionectomized eyes as seen in the detailed 9-day administration. The IOP always fell more in the normal eye, and the ganglionectomized eye IOP reduction was about 20% of that in the normal eye with SP-1 and about 40% of that in the normal eye with SP-106 (Table III). Random checks on the IOP fall during the weeks were also made and revealed similar patterns of reduction in both normal and ganglionectomized eyes. No evidence of tolerance is found in this data since the IOP is about the same for each drug on successive weekly readings (Table III).

TABLE I

Comparison of the IOP-lowering effect of Δ^9-THC delivered to the eye in four different oils

	Time	N.F. light mineral oil viscosity 11 cP RE	N.F. light mineral oil viscosity 11 cP LE	N.F. light mineral oil viscosity 14 cP RE	N.F. light mineral oil viscosity 14 cP LE	Diethylene glycol oleate† viscosity * cP RE	Diethylene glycol oleate† viscosity * cP LE	N.F. light mineral oil viscosity 26 cP RE	N.F. light mineral oil viscosity 26 cP LE
IOP	0	21·1 ± 0·7	21·6 ± 0·6	19·7 ± 0·5	20·3 ± 0·5	19·6 ± 0·6	20·3 ± 0·5	20·4 ± 0·7	19·8 ± 0·4
% Change in IOP	60	17·1 ± 1·2	5·1 ± 0·8	11·2 ± 1·1	8·9 ± 0·9	3·9 ± 0·4	+2·0 ± 2·1	10·4 ± 1·0	2·0 ± 1·2
	120	0·5 ± 1·1	+4·2 ± 0·9	3·6 ± 1·1	1·5 ± 0·3	12·0 ± 0·9	7·6 ± 1·2	9·1 ± 0·7	6·9 ± 1·2
	180	6·4 ± 1·3	2·8 ± 0·7	9·9 ± 1·0	7·6 ± 1·1	5·6 ± 1·2	6·4 ± 0·9	15·4 ± 1·1	7·9 ± 0·8
	240	6·6 ± 0·8	+4·2 ± 1·2	+1·0 ± 1·4	+7·1 ± 2·3	−3·4 ± 0·8	+4·6 ± 0·9	8·1 ± 1·4	1·5 ± 0·9

RE is normal, LE is ganglionectomized.

IOP is intraocular pressure preceding instillation of drop.

% Change in IOP is the percent change of the mean IOP of eight eyes from the initial IOP. Values are the mean ±S.E.M. All values are a reduction in IOP except for a − sign which indicates a rise in IOP relative to pre-drug values.

* Viscosity is unknown but is very viscous. † (Pegosperse, Glyco Chem. Co.).

Light mineral oil alone (a potential vehicle for cannabinoids) was also tested for irritation and shown to produce only a mild irritation. This took the form of lid redness each day, at about a level of 1 on the Draize scale (Draize, Woodard and Calvery, 1944) which upon overnight cessation of drops cleared completely. No conjunctival injection or edema was noted over 4 weeks with application 3×25 μl each day. The latter regimen was chosen to replicate the possible normal clinical application of the oil. Over the 9 weeks of treatment no animal showed more than mild lid redness with light mineral oil and 1% hydroxypropyl methylcellulose.

Intravenous SP-106 covering a range of doses was also given to other rabbits in separate experiments. The lowest effective dose was 50×10^{-6} mg/ml plasma which gave an IOP fall of 20% at peak time and caused an IOP fall for about 5 hr. As the

TABLE II

IOP fall caused by chronic (9-day) topical administration of SP-1 and SP-106 to rabbit eyes

	SP-1				SP-106			
	Day 1		Day 9		Day 1		Day 9	
	N	Gangx	N	Gangx	N	Gangx	N	Gangx
IOP_0	19·50	19·25	18·75	19·38	20·50	20·1	19·6	20·1
Changes in IOP								
30	12·82	5·19	8·00	+0·62	10·24	2·49	7·14	2·49
60	14·10	6·49	10·67	3·25	9·27	8·46	12·24	3·48
120	16·67	5·19	17·33	7·12	12·73	6·47	14·29	3·48
150	19·23	5·19	17·33	3·25	16·10	5·47	17·35	5·47
180	15·38	3·90	13·33	3·25	13·17	6·47	16·33	5·47
210	17·95	5·19	6·67	+3·20	18·05	4·48	16·33	0·50
240	12·82	0·00	9·33	1·96	14·15	6·47	8·16	+0·50
270	12·82	0·00	9·33	+0·62	15·12	7·46	12·24	1·50
300	12·82	3·90	14·67	0·67	17·07	5·47	12·24	+0·50
330	12·82	+0·13	9·33	+3·20	19·02	7·46	17·35	3·48
360	0·00	+5·19	9·33	0·67	11·22	+0·05	15·31	3·48
390	3·85	+0·39	16·00	1·96	2·40	+9·45	17·35	5·47
420	3·85	+3·90	9·33	0·67	6·34	+2·49	11·22	3·48

IOP_0 is the average IOP preceding the eye drop. All other values are the percent fall of the mean IOP of twelve eyes from the initial IOP for RE and LE, except for a + sign, which indicates a rise in IOP relative to pre-drug values. N, normal eyes, Gangx, ganglionectomized.

TABLE III

IOP fall at week 1 and week 9 caused by chronic (60 day) administration of SP-1 and SP-106 to rabbit eyes

	Week 1				Week 9			
	SP-1		SP-106		SP-1		SP-106	
Time	N	Gangx	N	Gangx	N	Gangx	N	Gangx
0	18·6	19·0	19·7	19·3	19·3	18·3	20·0	19·7
30	9	7	7	+1	5	5	10	10
60	13	5	12	2	19	8	21	10
120	17	8	12	1	11	7	20	10
180	14	0	11	1	22	7	16	7
240	6	+3	4	+1	16	4	12	5
300	+1	+3	4	+4	22	5	20	8
360	7	+1	8	+3	19	5	19	7
420	6	0	8	+4	14	2	17	7

IOP at time 0 is average initial IOP, all other values are the percent fall of the mean IOP of twelve eyes for SP-1 and twelve eyes for SP-106 from the initial IOP, except for those values preceded by a + sign which indicate an IOP greater than the pre-drug value. N, normal eyes, Gangx, ganglionectomized.

dose increased the IOP fall became both greater (Fig. 2) and of longer duration until a maximum fall of about 40% occurred, indicating a dose-response relationship similar to that seen with THC (Green and Bowman, 1976). Assuming complete absorption of the topically applied drug (50 μl of 0·1% = 0·05 mg) into the plasma the concentration would be 50×10^{-5} mg/ml plasma, above the minimum concentration needed to evoke an IOP fall. The IOP decrease with systemically and topically administered SP-106 is approximately the same.

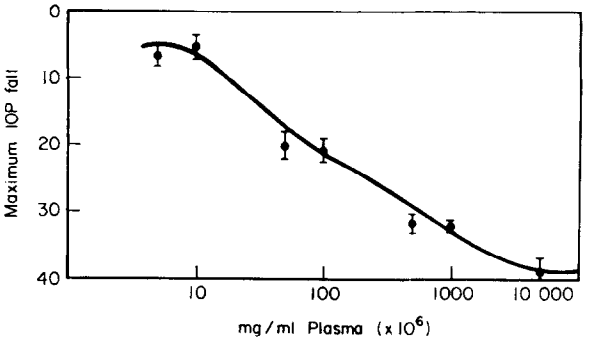

FIG. 2. Log-dose response curve of intravenous SP-106 against percentage fall in intraocular pressure. Values are the mean ±S.E.M. of twenty eyes.

4. Discussion

The ocular penetration data indicates that Δ^9-THC can penetrate into the eye, albeit in low concentrations (Fig. 1). The lowest in vitro dose level found to exert a significant effect on the ciliary epithelial permeability was 5×10^{-7} mg/ml (Green and Pederson, 1973) and the highest persistent concentrations found in the aqueous humor and iris are 0·5 and $1{\cdot}0 \times 10^{-7}$ μg/ml respectively, or about five times less than those concentrations causing a pronounced in vitro effect. Part of the THC effect, however, is caused locally in the eye (Green, Kim and Bowman, 1976; Green, Bigger, Kim and Bowman, 1976) and the penetration data indicate that the drug is, indeed, reaching the target tissues. The data obtained with radiolabeled drug applied only to one eye indicates that although the aqueous humor and cornea contain small quantities of drug which have been transferred by the vascular route, the iris contains a concentration about 70% of that seen in the eye receiving the drop. These findings, together with the plasma detection of significant quantities of THC, indicate the substantial vascular absorption.

No chromatographic analysis was performed on the samples since the ^{14}C-label is in a very stable position on the compound and remains firmly attached to the molecule (NIDA, personal communication). There may be some metabolism of the Δ^9-THC since it has been reported in rabbit after intravenous injection that the half life of Δ^9-THC is 7–16 min (Agurell, Nilsson, Ohlsson and Sandberg, 1970). The ^{14}C-label, however, would remain on an active metabolite, presumably a more polar compound, rather than being lost from the molecule. The second uptake peak concentration seen in iris resembles that seen in the liver following intravenous injection of Δ^9-THC (Agurell et al., 1970; Willinsky, Kalant, Meresz, Endrenyi and Woo, 1974). There are similarities between these tissues in terms of common types of organic transport systems (Bárány, 1973) and it may be that the second peak of activity represents an

active tissue uptake of blood-borne Δ^9-THC, which is illustrated also in the data above where only one eye received the THC and yet the contralateral iris contained almost 70% of the radioactivity in the ipsilateral iris.

The fluorescein staining pattern of the cornea revealed that no staining was visible with LMO, very light punctate staining with HMO (one cornea had a centrally located lesion), other light pitting with saline/Tween 80, diffuse staining with 80. The vehicle comparison serves to emphasize the data obtained on reduction of IOP. With THC in sesame oil a variable IOP fall was found, between 2 and 3 mmHg (Green and Bowman, 1976) but with THC in mineral oil the IOP fall is both consistent and extensive. It is of interest that the lowest viscosity oil containing Δ^9-THC was responsible for the greatest IOP falls since the reverse would be anticipated. It has been shown in other studies, however, that drug penetration and viscosity are not necessarily tightly linked (Adler, Maurice and Paterson, 1971; Green and Downs, 1975). Other aspects of the vehicle differences include the ability of the oil to release the drug as well as spreading within the conjunctival sac. Sesame oil also causes an effect on adrenergic synapses (Anton, Serrano, Beyer and Lavappa, 1974) as well as surface effects on the cornea and, despite its wide oral use for Δ^9-THC, has therefore, been replaced in our studies by light mineral oil as the vehicle of choice for topical ocular application of lipid soluble compounds.

Both SP-1 and SP-106 caused an IOP fall in the paired normal and ganglionectomized rabbit eye, although their effects were quantitatively different (Tables II and III). SP-1, the oil-soluble compound, generally caused a greater relative fall in normal eyes compared to SP-106, but SP-106 caused a greater relative fall in the ganglionectomized compared to the normal eye than SP-1 (Green et al., 1976). Whether the difference between SP-1 and SP-106 reflects greater biological activity of the compound in the eye or a difference between the vehicles awaits further study. The fact that the ganglionectomized eye showed a relatively greater fall with SP-106 (Table III), however, indicates that the local effect of this drug in the eye is greater while the central effect is reduced relative to SP-1 (Green et al., 1976). For ophthalmic use in a potential clinical situation, enhancement of the local and diminution of the central effect is desirable (Green, 1975) and SP-106 appears to be a suitable step in that direction. The fall in IOP in both eyes, however, highlights the systemic effect and action of these drugs.

No tolerance was noted over the 9- or 60-day periods to the daily regimen of drug application. Administration of either drug always resulted in a fall of IOP which was sustained and followed by another fall after the second drop, since the second drop was applied at a time when the IOP was rising towards base-line (Tables II and III). It is apparent, therefore, that for 8 hr IOP regulation a 2 drop regimen would suffice but for extended clinical control of IOP a 3 drop regimen would probably be needed if extrapolation from the rabbit to man is valid.

It has been reported in both man (Hepler, Frank and Petrus, 1976) and dog (Thompson and Yang, 1976) that there is decreased lacrimation after inhalation (Hepler et al., 1976) or oral administration (Thompson and Yang, 1976) of THC or other analogs. This was not noted in the present experiments, where topical drops of the nitrogen analogs were used, presumably because of the viscous nature of the two vehicles employed which remain on the eye for extended periods of time thus preventing evaporation: decreased lacrimation was only noted following the highest intravenous dose of SP-106. Indeed, if decreased lacrimation constitutes a significant clinical problem the use of a more viscid vehicle would tend to counteract this problem.

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