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Acute Dose Response of Intraocular Pressure to Topical and Oral Cannabinoids (39643)

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The primary active ingredient of marijuana, tetrahydrocannabinol (Δ^9-THC), causes a dose-dependent fall in intraocular pressure (IOP) when given intravenously to man (1) or rabbit (2). In addition, a dose-related fall in IOP is found after THC in sesame oil is applied topically to rabbit eyes (2). However, Δ^9-THC has psychoactive properties which render it unacceptable for widespread clinical use. Recently, newer nitrogen-containing analogs, *N*-substituted benzopyranopyridines, which are structurally related to the cannabinoids, have been synthesized, and have activity in many pharmacological tests similar to the parent compounds (3–5). A spectrum of new compounds has undergone pharmacological and toxicological screening in which some compounds show excellent clinical potential. We have measured the IOP of rabbits and monkeys in response to either a single topical drop or to a single oral dose of each of three of these new drugs to determine their IOP-lowering efficacy. Similar studies with two of these compounds (SP-1 and SP-106), applied topically to rabbit eyes in other vehicles, have been reported previously (6).

Materials and methods. Our studies were made on conscious adult albino rabbits (2 to 4 kg) of either sex. IOP was measured hourly with an Alcon Pneumotonograph, which had been calibrated for the rabbit eye: Determinations were made after application of a drop of 0.5% tetracaine hydrochloride which was washed off after 5 to 10 sec with at least 1 ml of saline solution. One drug, with an *N*-propargyl substitution on the C-ring and a dimethylheptyl branched alkyl side chain, is designated SP-1, is an oil-soluble nitrogen-containing compound structurally related to the cannabinoids (3–6), and was dissolved in a white, light paraffin oil (Fisher Scientific Company). Other benzopyranopyridines, designated SP-106 and SP-204, which are both water-soluble ester derivatives of SP-1 with differing side chains, were dissolved in a commercial artificial tear solution (Ultratears, Alcon Laboratories, Fort Worth, Texas). A baseline IOP was established in each experiment prior to use of the drugs in either rabbits or monkeys by two IOP readings at a 30-min interval: The two values were averaged as the baseline since they differed by less than 1 mm Hg. For topical administration one 50-μl drop of solution was applied unilaterally to one corneal surface, and for oral administration the drug was given in 10 ml of the appropriate vehicle through a stomach tube.

Results. The dose–response curves for the three compounds applied topically in the rabbit are shown in Fig 1. All drugs caused a fall in IOP compared to vehicle alone. The maximum fall in IOP occurred, almost without exception, at 120 min and returned to original baseline IOP at 6 hr with low drug concentrations (0.01%) but with 1% an IOP fall of between 5 to 10% was still present at 6 hr. The contralateral eye also showed a fall in IOP between 1 and 3% less than the treated eye although the time course of action was identical. Vehicle alone caused only a 1 to 3% reduction in IOP.

After oral administration to the rabbit the fall in IOP was not as marked as after topical administration at equivalent dose levels (mg/kg), which difference may represent less complete absorption from the intestine compared to that from orbital tissues. The dose–response curve (Table I) is much less steep than that seen after topical doses (Fig 1). SP-106 caused a more rapid fall in IOP than SP-1 (SP-204 was not tested in these experiments due to a shortage in supply). With SP-106 the effect was complete and baseline IOP regained at 7 hr, whereas SP-1 appeared to have a longer lasting effect which was of slower onset.

Studies in ketamine-immobilized juvenile (3 kg) rhesus monkeys (*M. mulatta*) indi-

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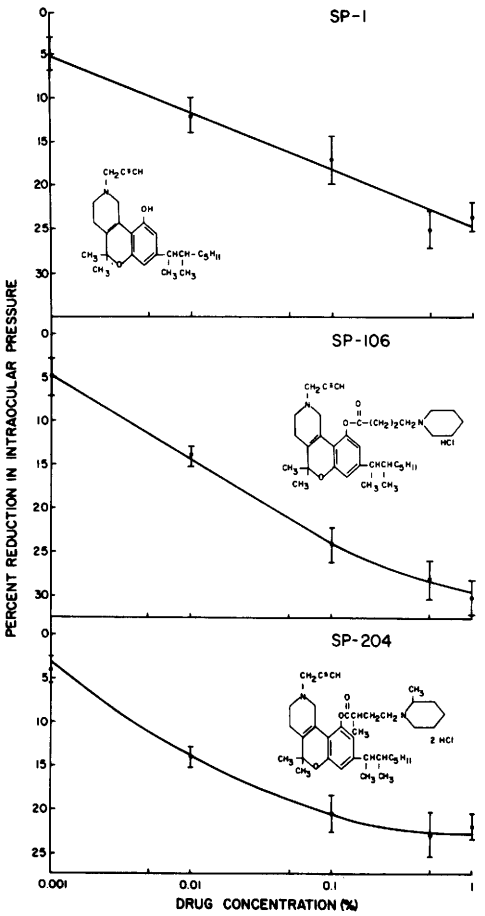

FIG. 1. Dose response of rabbit intraocular pressure to three topically applied nitrogen-containing compounds related to the cannabinoids. Each value is the mean ± the standard error of the mean of the maximum intraocular pressure fall for 10 treated eyes of 10 animals.

cated that 0.1% concentrations of these three drugs caused little change in IOP when applied topically (maximum 7% at 1 hr, mean of 5 animals, 10 eyes), but 0.5% caused a fall in IOP (maximum of 20% at 2 hr) of about 4 to 5 hr duration (Table II). Vehicle alone given to the eye caused only a maximum 1% fall in IOP. The regimen used was the same as that in the rabbit studies, with five monkeys used as treated and one as a control per test drug. The control animal was changed between experimental sessions, which were a minimum of 3 days apart. Since the IOP fell in both eyes, the data from both treated and untreated eyes were pooled. The need for a higher dose level in the monkey may be related to a higher metabolism of these compounds compared to the rabbit.

Discussion. The present data indicate that, when given acutely, the newer benzopyranopyridines tested all cause a fall in IOP of both the rabbit and monkey eye. There is a quantitative difference, however, in their effects and this is presumably another reflection of the differences they exert in a variety of tests. Some drugs appear, if side chains are modified, to elicit quantitatively different responses compared to the parent compound. The new compounds seem to demonstrate somewhat selective effects on different parameters (3–6), revealing different pharmacological spectra.

That the IOP falls in both eyes when administered only to one eye establishes the systemic absorption of these drugs, which has been noted previously for Δ^9-THC (7, 8). The difference in response of the contralateral eye is usually small, being between 1 and 3%.

Following oral drug administration more marked differences between the biological responses to the three drugs are seen. The IOP fall after SP-106 is more rapid in onset than that of SP-1 and this may be a reflection of either more rapid absorption of the water-soluble compound or better release of the compound from a water-based rather than a mineral-oil-based vehicle. Previous work on intraocular penetration of Δ^9-THC from different vehicles demonstrated that the release of the drug varied from vehicle to vehicle (9).

The higher concentration required in monkeys may be related to a more rapid metabolism of these compounds, thus higher dose levels of the cannabinoids would be required to produce a biological effect.

All three compounds reduce IOP by acting both locally in the eye (8, 9) and via a systemic route, since an untreated contralateral eye shows a fall in IOP. A locus of action is presumably some central site in the adrenergic nervous pathways (9), since both superior cervical ganglionectomy and preganglionectomy section of the cervical nerve reduce the IOP lowering effects of Δ^9-THC (7–9).

In an experimental animal there is no way

TABLE I. PERCENTAGE REDUCTION IN INTRAOCULAR PRESSURE IN THE RABBIT IN RESPONSE TO ORAL BENZOPYRANOPYRIDINES[a]

	SP-106				SP-1			
Time (min)	0.003 mg/kg	0.03 mg/kg	0.15 mg/kg	0.3 mg/kg	0.003 mg/kg	0.03 mg/kg	0.3 mg/kg	1.5 mg/kg
0[b]	21.9	21.0	21.1	20.6	21.0	21.1	21.0	20.0
60	3	11	12	11	9	10	7	4
120	3	14	12	17	6	15	13	3
180	8	11	12	12	4	10	16	17
240	4	13	12	5	5	14	17	19
300	3	6	9	1	2	10	11	18
360	2	2	3	1	1	5	8	16
420	1	+2	2	0	1	4	2	13

[a] The values represent the IOP fall in 10 normal eyes of 10 rabbits.

[b] The original baseline IOP in mm Hg (−30 min and 0 time prior to drug administration) is given in the first horizontal line. The largest SEM is ±2.3% (i.e., about 20% of the IOP fall, not shown for clarity). Data for the contralateral eye are not given as these eyes had been subjected to superior cervical ganglionectomy and, therefore, the IOP response was much reduced (7–8).

TABLE II. FALL IN INTRAOCULAR PRESSURE OF JUVENILE RHESUS MONKEY AFTER TOPICAL BENZOPYRANOPYRIDINES.[a]

	Percentage reduction in IOP		
Time (min)	SP-1 0.5%	SP-106 0.5%	SP-204 0.5%
0[b]	19.20	19.75	19.75
60	13	12	12
120	17	16	13
180	15	16	11
240	13	11	19
300	5	9	13
360	1	3	11

[a] The values represent the IOP fall in at least eight eyes, the data from both eyes is used since the IOP fall in the untreated eye differed little from that in the treated eye.

[b] The original baseline IOP in mm Hg (−30 min and 0 time, prior to drug administration) is given in the first horizontal line. The largest SEM is ±2.5%.

to discern whether or not the euphoric/dysphoric effects of these drugs are revealed and this will only be determined by testing in man. Preliminary data (10) indicate that dose levels greater than 0.06 to 0.1 mg/kg of SP-106 when given orally were required to elicit any noticeable subjective effects in human volunteers. This compares to the present studies where dose levels of 0.01 mg/kg (topical in rabbit), 0.08 mg/kg (topical in monkey), or 0.02 mg/kg (oral in rabbit) were found to produce pronounced IOP reductions. If further testing shows that the psychoactive properties of these compounds are found to be minimal or absent at dose levels required to reduce IOP then these compounds may be of some value clinically to reduce elevated IOP. The IOP fall is as good or better than presently available drugs (11) and the benzopyranopyridines appear to offer a favorable alternative to current topical therapy.

Summary. Three nitrogen-containing cannabinoids caused a dose-dependent fall of intraocular pressure when administered either topically or orally to rabbits. Concentrations of 0.001 to 1% applied topically and 0.3 mg/kg orally were effective. Topical concentrations of 0.5% caused a substantial decrease of intraocular pressure in rhesus monkeys. These compounds may prove therapeutically useful in the treatment of elevated intraocular pressure.

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