JOUNELA, A., SAARNIVAARA, L. & AHTEE, L. (1971). *Scand. J. clin. Lab. Invest.*, **27**, *Suppl.* 116, 74.
MARSHALL, I. & GRAHAME-SMITH, D. G. (1970). *Nature, Lond.*, **228**, 1206–1208.
MEEK, J. & WERDINIUS, B. (1970). *J. Pharm. Pharmac.*, **22**, 141–143.
MURPHY, D. L., COLBURN, R. W., DAVIS, J. M. & BUNNEY, W. E. Jr. (1969). *Life Sci.*, **8**, 1187–1193.
NEFF, N. H., TOZER, T. N. & BRODIE, B. B. (1967). *J. Pharmac. exp. Ther.*, **158**, 214–218.
ROGERS, K. J. (1971). *Europ. J. Pharmac.*, **14**, 86–88.
ROGERS, K. J. & THORNTON, J. A. (1969). *Br. J. Pharmac.*, **36**, 470–480.
SHARMAN, D. F. (1969). In: *Metabolism of amines in the brain*, pp. 34–37. Editor: Hooper, G. London: Macmillan & Co Ltd.
SHEN, F.-H., LOH, H. H. & WAY, E. L. (1970). *J. Pharmac. exp. Ther.*, **175**, 427–434.
TAKAGI, H. & NAKAMA, M. (1966). *Jap. J. Pharmac.*, **16**, 483–484.
TAMARKIN, N. R., GOODWIN, F. K. & AXELROD, J. (1970). *Life Sci.*, **9**, 1397–1408.
TENEN, S. S. (1967). *Psychopharmacologia*, **10**, 204–219.
TENEN, S. S. (1968). *Ibid.*, **12**, 278–285.
VOGT, M. (1954). *J. Physiol., Lond.*, **123**, 451–481.

Comparison of four vehicles for intraperitoneal administration of Δ^1-tetrahydrocannabinol*

Recently there has been much interest in research on Δ^1-tetrahydrocannabinol, commonly designated by the abbreviation Δ^1-THC (or Δ^9-THC), which is believed to be the principal active constituent of marihuana. However, a practical difficulty of research with Δ^1-THC is its insolubility in water and many other common solvents. It is soluble in ethanol, but this vehicle is pharmacologically active, in particular resembling effects of Δ^1-THC in general depressant action (Kubena & Barry, 1970) and in stimulation of the adrenal-pituitary system (Kubena, Perhach & Barry, 1971). Another solvent for Δ^1-THC, propylene glycol, was used by Bose, Saifi & Bhagwat (1964) and by Bicher & Mechoulam (1968), but this is also a general depressant when given in large amounts (Bost & Ruckebusch, 1962). Therefore, in the studies cited and others (Sofia & Barry, 1970; Sofia, Dixit & Barry, 1971), the present authors used a suspension in 10% propylene glycol, 1% polysorbate (Tween) 80 and isotonic saline to minimize the amount of propylene glycol administered.

Fenimore & Loy (1971) have recently suggested the use of a suspension of Δ^1-THC in polyvinylpyrrolidone (PVP), a plasma expander. Other vehicles used for intraperitoneal administration of Δ^1-THC include a suspension in bovine serum albumin (Dewey, Peng & Harris, 1970; McMillan, Harris & others, 1970) and a suspension in Tween 80-saline (Holtzman, Lovell & others, 1969). Recently, Ho, Fritchie & others (1971) presented evidence for poor absorption of Δ^1-THC after intraperitoneal injection in a Tween-80-saline suspension. They recommended that the drug be administered intravenously, but this route has the drawback of being more difficult and stressful, especially for rats, and not directly comparable with data on other drugs, which are mostly administered intraperitoneally.

The present report compares four vehicles in efficacy and duration of effect after intraperitoneal injection of Δ^1-THC. The latency to convulsion in mice following a maximal electroconvulsive shock (ECS) was used as a bioassay of the Δ^1-THC effect. Recent work (Sofia, Solomon & Barry, 1971) has shown this to be a sensitive measure of Δ^1-THC, even at a low dose, when injected intraperitoneally in a 10% propylene glycol–1% Tween 80-saline suspension.

The experiment was made on 384 male albino mice (Swiss-Webster), 20 to 22 g (Hilltop Lab Animals, Inc., Scottdale, Pa.). They were divided randomly among the

*Numbered Δ^9 according to IUPAC rules.

four vehicle conditions: bovine serum albumin-saline (BSA), 1% Tween 80-saline (Saline), polyvinylpyrrolidone-saline (PVP), and 10% propylene glycol-1% Tween 80-saline (PG). For all the vehicles the volume of fluid injected was 0·1 ml/10 g (10 ml/kg), containing Δ^1-THC in a concentration of 1 or 4 mg/ml depending on the dosage (10 or 40 mg/kg).

The BSA was prepared in a solution of 50 mg/ml in isotonic saline. The Saline vehicle was also isotonic and included a 1% suspension of Tween 80. The Δ^1-THC, received from the FDA-NIMH Psychotomimetic Drugs Advisory Committee in a 99% ethanol solution (100 mg/ml), was flash evaporated and within 10 min added to the vehicle. For the PG vehicle the flash-evaporated Δ^1-THC was dissolved in 100% propylene glycol (10 or 40 mg/ml), to which the other fluids were immediately added to make up a suspension of Δ^1-THC in 1% Tween 80 and 10% propylene glycol in isotonic saline. For the PVP vehicle, the original ethanol solution of Δ^1-THC (10 or 40 mg) was added to 300 mg of PVP in a 95% ethanol solution (100 mg/ml). The ethanol was flash evaporated and sufficient isotonic saline was added to make up a suspension containing 30 mg/ml of PVP.

These four vehicle groups were subdivided into groups tested at four time intervals after intraperitoneal injection (0·25, 1, 2, 6 h). Half the animals were injected with the vehicle alone (control), half with Δ^1-THC suspended in the vehicle. Half the animals, tested on one day, were equally divided between control and the lower dose of Δ^1-THC (10 mg/kg). The other half were divided between control and the higher dose of Δ^1-THC (40 mg/kg). Each of the animals tested on the same day were housed in the laboratory in groups of 12 for 24 h before use and were divided at the time of injection into 6 vehicle and 6 drug animals. The mice were tested for latency to tonic convulsion, i.e. complete extension of the hind limbs, on electroshock of 50 mA intensity, 0·2 s duration, applied transcorneally. Latency to tonic extension was recorded by stopwatch in 0·1 s units.

Table 1. *Effects of Δ^1-THC on latency to convulsion (mean ± s.e.) at four time intervals after intraperitoneal injection in four vehicles.*†*

Vehicle	Time (h)	Δ^1-THC			% Difference from control	
		Control N = 12	10 mg/kg N = 6	40 mg/kg N = 6	10 mg/kg	40 mg/kg
BSA	0·25	1·50 ± ·08	1·60 ± ·21	1·77 ± ·11	7	18
	1	1·52 ± ·11	1·62 ± ·20	1·95 ± ·21	7	28
	2	1·50 ± ·08	1·28 ± ·07	1·53 ± ·10	—15	2
	6	1·32 ± ·08	1·35 ± ·05	1·53 ± ·12	2	16
Saline	0·25	1·30 ± ·04	1·48 ± ·16	1·65 ± ·13	14	27*
	1	1·46 ± ·09	1·42 ± ·12	1·70 ± ·07	—3	16
	2	1·69 ± ·11	1·48 ± ·11	1·53 ± ·11	—12	—9
	6	1·48 ± ·11	1·63 ± ·21	1·55 ± ·07	10	5
PVP	0·25	1·47 ± ·08	1·97 ± ·16	2·17 ± ·17	34*	48**
	1	1·53 ± ·09	1·78 ± ·05	3·77 ± ·52	16	146**
	2	1·46 ± ·06	1·65 ± ·10	2·92 ± ·40	13	100
	6	1·38 ± ·06	1·50 ± ·07	1·50 ± ·09	9	9
PG	0·25	1·54 ± ·08	2·32 ± ·20	3·63 ± ·36	51**	136**
	1	1·53 ± ·05	2·03 ± ·20	4·83 ± ·17	33*	216**
	2	1·48 ± ·08	2·07 ± ·16	4·57 ± ·41	40*	209**
	6	1·48 ± ·06	1·75 ± ·14	2·13 ± ·25	18	44*

† A maximum interval of 5 s was recorded for animals which failed to convulse by that time (2 on PVP at 1 h, 5 on PG at 1 and 4 on PG at 2 h, all after 40 mg/kg Δ^1-THC).

* $P < 0·01$ for difference from control.

** $P < 0·001$ for difference from control.

BSA = bovine serum albumin. Saline = 1% Tween 80-saline. PVP = polyvinylpyrrolidone-saline. PG = 10% propylene glycol 1% Tween 80-saline.

Table 1 summarizes the results of the experiment. The control animals tested on different days, for comparison with different doses of Δ^1-THC, showed no statistically significant differences from each other and are combined into a single group of 12 animals under each experimental condition. There was no reliable difference among the four vehicles without the drug; the last two columns of the Table show that Δ^1-THC generally increased latency of the ECS response, with a much larger effect of the higher dose and with differences among the vehicles.

In each of the eight conditions comprising both dose levels and all four time intervals, the percentage increase in latency was larger for the PG than any of the other three vehicles. The PVP was the second most effective vehicle, and at the first three time intervals a larger increase was invariably found with PVP than with either of the other two vehicles. The peak effect for both PG and PVP was at 0·25 h with 10 mg/kg and at 1 h with 40 mg/kg, indicating a somewhat earlier time of peak action with the lower dose. The other vehicles (BSA, Saline) showed very little difference from control; the only reliable difference was with the high Δ^1-THC dose at 0·25 h with the Saline vehicle.

The failure of Δ^1-THC absorption from the peritoneal cavity, reported by Ho & others (1971) with the saline vehicle, is confirmed and extended to the BSA vehicle in the present study. Observations indicated that both of these vehicles failed to form satisfactory Δ^1-THC suspensions. The PVP forms an effective suspension but being a larger molecule than PG might not be absorbed readily from the peritoneal cavity. The PG vehicle was also observed to form an effective suspension, and the present data indicate that it is the vehicle of choice for intraperitoneal administration of Δ^1-THC.

This work was supported in part by PHS grants GM-1217 and MH-13595 and Research Scientist Development Award K2-MH-5921.

Department of Pharmacology,
University of Pittsburgh School of Pharmacy,
Pittsburgh, Pennsylvania 15213, U.S.A.

R. DUANE SOFIA
ROBERT K. KUBENA
HERBERT BARRY, III

July 2, 1971

REFERENCES

BICHER, H. I. & MECHOULAM, R. (1968). *Archs int. Pharmacodyn. Thér.*, **172**, 24–31.

BOSE, B. C., SAIFI, A. Q. & BHAGWAT, A. W. (1964). *Ibid.*, **147**, 291–297.

BOST, J. & RUCKEBUSCH, Y. (1962). *Thérapie*, **17**, 83–94.

DEWEY, W. L., PENG, T.-C. & HARRIS, L. S. (1970). *Europ. J. Pharmac.*, **12**, 382–384.

FENIMORE, D. C. & LOY, P. R. (1971). *J. Pharm. Pharmac.*, **23**, 310.

HO, B. T., FRITCHIE, G. E., ENGLERT, L. F., MCISAAC, W. M. & INDANPAAN-HEIKKILA, J. E. (1971). *Ibid.*, **23**, 309–310.

HOLTZMAN, D., LOVELL, R. A., JAFFE, J. H. & FREEDMAN, D. X. (1969). *Science, N.Y.*, **163**, 1464–1467.

KUBENA, R. K. & BARRY, H., III (1970). *J. Pharmac. exp. Ther.*, **173**, 94–100.

KUBENA, R. K., PERHACH, J. L. & BARRY, H., III (1971). *Europ. J. Pharmac.*, **4**, 89–92.

MCMILLAN, D. E., HARRIS, L. S., FRANKENHEIM, J. M. & KENNEDY, J. S. (1970). *Science, N.Y.*, **169**, 501–503.

SOFIA, R. D. & BARRY, H., III (1970). *Europ. J. Pharmac.*, **13**, 134–137.

SOFIA, R. D., DIXIT, B. N. & BARRY, H., III (1971). *Life Sci.*, **10**, 425–436.

SOFIA, R. D., SOLOMON, T. S. & BARRY, H., III. (1971). *Pharmacologist*, **13**, 246.