European Journal of Pharmacology, 35 (1976) 7—16

ANTICONVULSANT ACTIVITY OF Δ^9-TETRAHYDROCANNABINOL COMPARED WITH THREE OTHER DRUGS*

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Received 30 June 1975, accepted 31 July 1975

R.D. SOFIA, T.A. SOLOMON and H. BARRY, III, *Anticonvulsant activity of Δ^9-tetrahydrocannabinol compared with three other drugs*, European J. Pharmacol. 35 (1976) 7—16.

Δ^9-Tetrahydrocannabinol (THC) was compared with diphenylhydantoin (DPH), phenobarbital (PB) and chlordiazepoxide (CDP) using several standard laboratory procedures to determine anticonvulsant activity in mice, i.e., the maximal electroshock test (MES), and seizures induced by pentylenetetrazol, strychnine and nicotine. In the MES test, THC was the least potent and DPH the most potent blocker of hind limb tonic extensor convulsions whereas THC was the most potent and DPH the least potent in increasing the latency to this response and in preventing mortality. Seizures and mortality induced by pentylenetetrazol or by strychnine were enhanced by THC and DPH and were blocked by PB and CDP. In the test with nicotine, none of the four anticonvulsant agents prevented seizures; DPH was the only one which failed to increase latency; THC and DPH were less potent than PB and CDP in preventing mortality. THC most closely resembled DPH in the tests with chemical convulsant agents, but a sedative action of THC, resembling that of PB and CDP, was indicated by low ED_{50} for increased latency and for prevention of mortality in the MES test.

Chemically induced convulsions
Δ^9-Tetrahydrocannabinol (THC)
Diphenylhydantoin (DPH)
Electroshock convulsions
Chlordiazepoxide (CDP)
Phenobarbital (PB)

1. Introduction

Loewe and Goodman (1947) reported on the anticonvulsant activity of some constituents of marihuana, measured by inhibition of the convulsions produced by maximal electroshock (MES). They concluded that the anticonvulsant action of crude marihuana extract was similar to that of diphenylhydantoin since neither drug protected against pentylenetetrazol-induced seizures. In a more recent study (Garriott et al., 1968) a constituent of marihuana, Δ^9-tetrahydrocannabinol (THC) and several of its analogs were shown to diminish the convulsive response to MES. However, no ED_{50} values for the anticonvulsant activity of crude marihuana or THC were presented in either of these studies.

The synthesis of pure Δ^9-tetrahydrocannabinol (THC), or Δ^1-tetrahydrocannabinol according to the alternative formal rather than monoterpenoid numbering system, has stimulated research on this and other effects of this principal active constituent of marihuana (Bur-

* The research comprised a portion of the Ph.D. Dissertation by R. Duane Sofia at the University of Pittsburgh and was supported by Public Health Service Training Grant GM-1217 from the National Institute of General Medical Sciences and by Research Grant MH-13595 and Research Scientist Development Award K2-MH-5921 to Herbert Barry, III from the National Institute of Mental Health.
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stein, 1973). Anticonvulsant effects of THC, measured by latency to maximal electroshock seizure, have been used as a bioassay for comparing suitable vehicles (Sofia et al., 1971a) and various routes of administration (Sofia et al., 1974). Other measures of anticonvulsant effects of THC have been studied by several investigators using various species of laboratory animals (Fujimoto, 1972; Killam and Killam, 1972; Boggan et al., 1973; Carlini et al., 1973; Chesher and Jackson, 1974; Consroe and Man, 1973; Consroe et al., 1973; Corcoran et al., 1973; Fried and McIntyre, 1973; Izquierdo and Orsingher, 1973; Karler et al., 1973; Wada et al., 1973; Karler et al., 1974a,b,c; McCaughran et al., 1974; Turkanis, 1974). Contrary to these findings Meldrum et al. (1974) were unable to confirm the anticonvulsant effect of THC reported earlier by Killam and Killam (1972) in the photosensitive baboon.

The present paper reports on a more comprehensive and detailed examination of the anticonvulsant properties of pure, synthetic THC by using several measures of electrically induced MES and several methods of chemically induced seizures. In order to measure relative potency, the effects of THC were compared with three clinically useful anti-epileptic drugs, namely, diphenylhydantoin (DPH), phenobarbital (PB) and chlordiazepoxide (CDP). A brief, preliminary report of this study was previously given (Sofia et al., 1971).

2. Materials and methods

2.1. Materials

2.1.1. Animals

The experiments were conducted on a total of 1,288 male, albino Swiss-Webster mice weighing 16—26 g. They were obtained from Hilltop Laboratories, Scottdale, Pennsylvania, and housed in groups of 8 animals each for no less than 5 days before the experiments were performed.

2.1.2. Drugs

Pure synthetic Δ^9-tetrahydrocannabinol (THC) was received in a 99% ethanol solution which in turn was flash evaporated at 50° C using a vacuum rotary evaporator until a constant weight was achieved. The oily, viscous, amber residue representing THC was immediately resolubilized in 100% propylene glycol in a concentration of 100 mg/ml and this stock solution was kept in a dark environment at −4° C. Immediately before its use the desired amount of THC was withdrawn from the stock solution and suspended in a 1% polysorbate 80 (Tween 80) isotonic saline solution to a final propylene glycol concentration of 10% permitting a volume of 0.1 ml/10 g (10 ml/kg) of body weight to be injected by the i.p. route. Except when specified otherwise (in *2.2.3.*), all control animals received the same quantities of propylene glycol, saline and polysorbate 80 as were contained in the respective THC solutions. Sofia et al. (1971a, 1974) found this vehicle superior to three others tested for administration of THC by the i.p. route.

Various doses of DPH sodium, PB sodium and CDP hydrochloride were each prepared (as the salt) in a concentration which allowed i.p. administration of a volume of 10 ml/kg. They were dissolved in distilled water except when specified otherwise (in *2.2.3.*).

2.2. Methods

2.2.1. Maximal electroshock seizures (MES)

Various doses of THC or its vehicle and of DPH, PB and CDP or their vehicles were administered 30 min prior to transcorneal administration of an electroshock of 50 mA intensity and 0.2 sec duration. The method and apparatus were the same as described by Swinyard et al. (1952) and used by Sofia et al. (1971a, 1974). The criterion for an anticonvulsant effect was abolition of tonic extension of the hind limbs. Latency to this response was measured by stopwatch to the nearest 0.1 sec. Animals not displaying tonic extensor seizures within 5 sec after delivery of the electroshock were considered protected from MES. Mortalities were recorded 10 min following administration of the shock. A total of

424 mice (53 groups of 8 each) were used in these experiments.

2.2.2. Duration of THC effect

The response to MES was tested by the procedures already described at one of 7 time intervals (0.25, 0.5, 1, 2, 4, 8 or 24 hr) after i.p. injection of a high THC dose (80 mg/kg) or at 0.5 hr after the vehicle for THC. A total of 64 mice (8 groups of 8 each) were used.

2.2.3. Different vehicles and time intervals

The response to MES was tested by the procedures already described at 0.5 or 2.0 hr after i.p. injection of vehicle or 1 of the 4 drugs (THC, 40 mg/kg; DPH, 15 mg/kg; PB, 25 mg/kg; CDP, 35 mg/kg). The doses chosen approximated the ED_{50} for preventing tonic hind limb extension to MES shown in table 1. The vehicle for THC was the same as already described (10% propylene glycol—1% polysorbate 80—saline) but all the other treatments were divided equally between groups assigned to this vehicle or distilled water. All treatments were subdivided into groups tested at 0.5 or 2.0 hr after injection. These procedures required a total of 144 mice (18 groups of 8 each).

2.2.4. Pentylenetetrazol-induced seizures

These experiments were conducted using a modification of the method described by Everett and Richards (1944). Pentylenetetrazol (Metrazol) directly stimulates excitatory neurons in the midbrain region (Lewin and Esplin, 1961). Therefore, protection against seizures induced by this chemoconvulsant might be attributed to a drug effect within this brain site. Groups of mice were pretreated i.p. with various doses of THC and each of the other drugs, followed 30 min later by an 85 mg/kg s.c. injection of pentylenetetrazol (in a volume of 10 mg/kg body weight) which represents the ED_{97}, i.e., the dose at which 97% of the animals display clonic-tonic convulsions (Swinyard et al., 1952). Protection against convulsions and the lethal effects of pentylenetetrazol as well as the latency to seizure occurrence were recorded up to 1 hr following administration of the chemoconvulsant. 19 groups of 8 mice each (a total of 152) were used in this series of experiments.

2.2.5. Strychnine-induced seizures

Strychnine acts at the level of the spinal cord (Bradley et al., 1953) by blocking only central postsynaptic inhibition (Curtis, 1963). Therefore, protection against this type of seizure would suggest a depression of neural activity in the spinal cord. Groups of mice were pretreated with various doses of the test drugs. Following a 30-min absorption time interval, strychnine sulfate (3 mg/kg) was given i.p. (in a volume of 10 mg/kg body weight) by the method of Everett and Richards (1944). Protection against tonic-clonic seizures and the lethal effects of strychnine as well as the latency to convulsion were recorded for 30 min following administration of the chemoconvulsant. A total of 248 mice (31 groups of 8 each) were required for this study.

2.2.6. Nicotine-induced seizures

The method used in these experiments was described by Yamamoto et al. (1966). Various doses of THC, DPH, PB and CDP were administered i.p. followed in 30 min by 20 mg/kg of nicotine · HCl, also administered i.p., in a volume of 10 mg/kg. The mice were observed throughout the ensuing one hr to determine the latencies to tonic convulsions and death, and the number of animals protected against these occurrences. A total of 256 mice (32 groups of 8 each) were employed in this segment of the investigation.

2.2.7. Statistics

Mean latencies to convulsions and death were calculated and reliability of differences among the groups measured by the Student's *t*-test for data obtained from each experiment. In addition, the method of Litchfield and Wilcoxon (1949) was used to estimate ED_{50} values.

3. Results

3.2.1. Effect on MES

The left-hand column of numbers in table 1 summarizes the protective effect of 4 test compounds on maximal electroshock (MES). 3 different measures are shown with the ED_{50} and 95% confidence limits calculated for each compound, separately for each measure: prevention of tonic convulsion, increased latency (defined as a latency 1.5 sec or greater for an individual mouse), and prevention of mortality. The different measures show different relative potencies of the compounds. THC was the least potent for preventing tonic convulsion as indicated by the highest ED_{50}. However, THC was the most potent for increasing latency and for preventing lethal effect as indicated by the lowest ED_{50} values for both of these parameters. PB was another compound with a relatively high ED_{50} on the first measure, but low ED_{50} values for preventing mortality and especially for increasing latency of convulsion. By contrast, DPH was the most potent of the 4 compounds in preventing convulsion but the least potent in preventing mortality.

Fig. 1 shows the dose–response curves for each of the 4 compounds for latency to hind limb tonic convulsion, with a maximal time of 5.0 sec assigned to the animals which showed no response. This measure is calculated only for those animals which convulsed and thus is independent of the measure of prevention of convulsion (table 1). The control values in fig. 1 show clearly that latencies longer than 1.5 sec are indeed unusually long. THC was the only one of the 4 compounds to produce an average latency longer than 1.5 sec at a dose as low as 1.25 mg/kg. At higher doses all 4 compounds showed a generally increasing latency. At a dose of 10 mg/kg, below the ED_{50} for prevent-

TABLE 1

ED_{50} (±95% Confidence Limits) in mg/kg, i.p., for anticonvulsant effects of Δ^9-tetrahydrocannabinol (THC), diphenylhydantoin (DPH), phenobarbital (PB), and chlordiazepoxide (CDP), using three measures (prevention of seizure, increased latency seizure, and prevention of mortality) against four convulsant agents (MES, pentylenetetrazol, strychnine, nicotine).

Drug	MES 50 mA, 0.2 sec	Pentylenetetrazol 85 mg/kg s.c.	Strychnine 30 mg/kg i.p.	Nicotine 20 mg/kg i.p.
Prevention of tonic hind limb extension				
THC	43.8 (29.2–65.6)	>120.0	>80.0	>120.0
DPH	12.6 (9.6–16.6)	>200.0	>80.0	>160.0
PB	25.0 (20.3–30.4)	10.0 (5.6–18.0)	19.1 (12.5–29.2)	>120.0
CDP	35.5 (25.9–48.6)	3.6 (2.3–5.7)	18.6 (12.5–28.8)	> 80.0
Increased latency of tonic hind limb extension				
THC	0.8	<10.0	45.0	9.0
DPH	3.1	25.0	>80.0	>160.0
PB	1.7	3.8	6.5	8.2
CDP	4.8	1.4	8.0	3.5 (1.1–6.0)
Prevention of mortality				
THC	1.0 (0.6–1.6)	*	>80.0	73.1 (51.1–104.6)
DPH	4.2 (2.9–6.1)	*	>80.0	98.0 (64.9–148.1)
PB	2.5 (1.3–5.0)	<2.5	8.9 (5.6–14.2)	55.0 (34.5–87.2)
CDP	2.6 (1.7–4.0)	<0.5	16.9 (10.4–27.6)	14.3 (8.7–23.6)

* Enhanced mortality, shown in fig. 3.

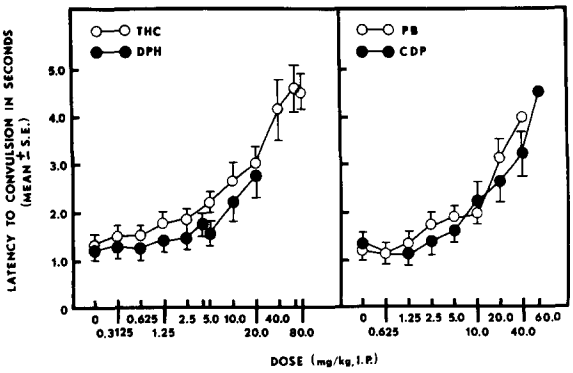

Fig. 1. Effects of Δ^9-Tetrahydrocannabinol (THC), Diphenylhydantoin (DPH), Phenobarbital (PB) and Chlordiazepoxide (CDP) on latency to tonic hind limb extension after maximal electroconvulsive shock (MES).

ing tonic hind limb convulsion (table 1), average latency was increased to above 2.0 sec by all the compounds except PB (fig. 1).

The ED_{50} for preventing mortality shown in table 1 was in general slightly higher than for increased latency, indicating that mortality was a somewhat less sensitive measure. However, CDP showed an opposite trend, with a higher ED_{50} for increasing latency than for preventing mortality. Fig. 1 shows that CDP tended to have less effect than PB on latency at the low doses of 2.5 and 5 mg/kg.

3.2.2. Duration of THC effect

Table 2 summarizes a further study on the duration of effect of a high dose of THC (80 mg/kg) at a wide range of time intervals after injection. The smallest percentage of convulsions was at 0.5 hr, and the difference from the vehicle, measured by the Fisher Exact Test, was statistically significant also at 0.25 and 1 hr. The average latency to convulsion in sec at the various time intervals was calculated only for those animals which convulsed to provide an independent measure of anticonvulsant activity. With this measure the maximal effect of THC was at 0.25 hr after administration, and the effect progressively decreased with time, although continuing to be statistically significant at 8 hr. At 24 hr the latency was slightly shorter than the vehicle average. Mortality was abolished in all groups tested in the first 4 hr. The large decrease seen also at 8 hr was not statistically significant, and at 24 hr there was an interesting but not statistically significant higher percentage mortality than for the vehicle condition.

3.2.3. Different vehicles and time intervals

Table 3 shows the comparison between the two time intervals (0.5 and 2.0 hr) for groups given 1 of the 2 vehicles (distilled water or propylene glycol). The percentage convulsing in table 3 shows close correspondence to the ED_{50} in table 1 determined under the same conditions (0.5 hr after propylene glycol for THC and after distilled water for the other three drugs). The independent measure of la-

TABLE 2

Percentage of animals convulsing, mean latency to convulsion in sec (±S.E.), and percentage mortality, in groups of 8 mice tested at 0.5 hr after the vehicle and at several time intervals after THC (80 mg/kg i.p.)

Condition	Vehicle	THC	THC	THC	THC	THC	THC	THC
Interval (hr)	0.5	0.25	0.5	1	2	4	8	24
% Convulsing	100	38*	13**	25**	88	100	100	100
Latency	1.33	4.10**	3.60**	3.40**	3.26**	2.35**	1.79**	1.26
(S.E.)	(0.10)	(0.32)	(0.0)	(0.20)	(0.33)	(0.26)	(0.18)	(0.07)
% Mortality	63	0*	0*	0*	0*	0*	13	88

* $p < 0.05$ compared with vehicle-treated group.
** $p < 0.01$ compared with vehicle-treated group.

TABLE 3

Comparison between 2 vehicles (water and propylene glycol) and 2 time intervals (0.5 and 2.0 hr) in tests for anticonvulsant effects of THC, DPH, PB, and CDP, measured by percentage of animals convulsing and latency to convulsion (mean in sec ± S.E.) in groups of 8 mice.

Drug	Dose mg/kg	Water		Propylene glycol	
		0.5 hr	2.0 hr	0.5 hr	2.0 hr
Percentage convulsing					
Vehicle	—	100	100	100	100
THC	40	—	—	50	75
DPH	15	50	50	38	50
PB	25	38	88	38	75
CDP	35	50	75	38	75
Latency to convulsion (mean ± S.E.)					
Vehicle	—	1.91 (0.13)	1.85 (0.20)	1.80 (0.21)	1.45 (0.11)
THC	40	—	—	4.00 (0.49)	3.70 (0.34)
DPH	15	3.13 (0.58)	3.23 (0.27)	3.67 (0.55)	3.80 (0.39)
PB	25	3.73 (0.67)	2.89 (0.39)	4.00 (0.60)	2.91 (0.38)
CDP	35	4.10 (0.26)	2.97 (0.43)	4.27 (0.58)	3.07 (0.39)

tency for the animals which convulsed, shown in table 3, indicates a marked effect of all 4 drugs, in accordance with the low ED_{50} for this measure shown in table 1. The low ED_{50} for prevention of mortality (table 1) is likewise supported by the fact that none of the animals died when the MES was preceded by any of the four drugs at the doses shown in table 3, whereas combining both time intervals, 63% died in the groups tested after the water vehicle alone and 50% died in the groups tested after the propylene glycol vehicle.

A comparison between the groups injected with water and propylene glycol indicates only a slight and inconsistent effect of the vehicle. No statistically significant difference between the two vehicles was found for either measure or for any of the drug conditions shown in table 3.

A comparison between the two time intervals indicates greater potency at 0.5 than at 2.0 hr for all the drugs except DPH. Combining both vehicles, convulsion was observed in 6 of the 16 mice (38%) tested at 0.5 hr after PB compared with 13 of the 16 mice (81%) tested at 2.0 hr after the same drug. This difference is statistically reliable ($\chi^2 = 4.66$, df = 1, $p < 0.05$). Table 3 shows for CDP a substantial difference in the same direction although not statistically significant. Combining both vehicles, the mean latency to convulsion in table 3 was reliably longer at 0.5 hr after CDP (4.17 ± 0.22, $n = 7$) than at 2.0 hr (3.02 ± 0.28, $n = 12$), $t = 2.77$, df = 17, $p < 0.05$. A non-significant difference in the same direction was found for THC and PB.

3.2.4. Effect on pentylenetetrazol-induced seizures

The second column of numbers in table 1 shows the effects of each of the 4 compounds on seizures induced by pentylenetetrazol. Both PB and CDP had protective effects, preventing tonic convulsions at lower doses than with MES, and also increasing the latency to tonic extension and preventing mortality at low doses. However, the other 2 compounds were ineffective as protective agents. Both THC and DPH failed to prevent the tonic convulsions

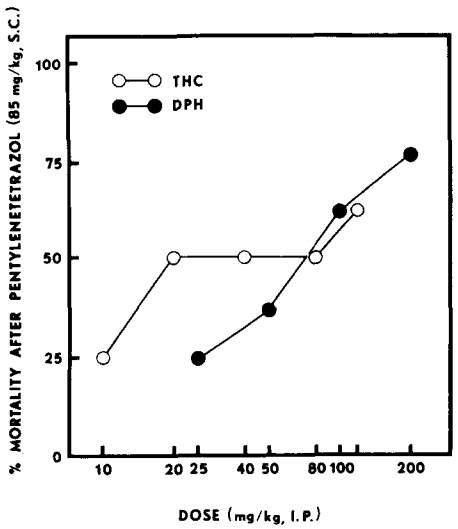

Fig. 2. Effects of i.p. administration of THC and DPH on mortality in mice induced by pentylenetetrazol (85 mg/kg, s.c.).

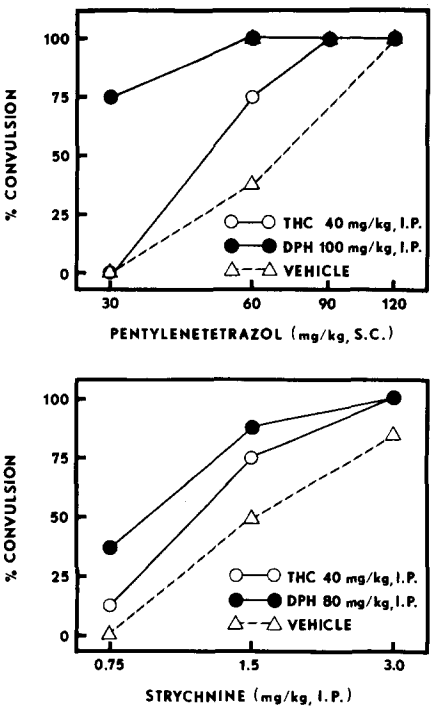

Fig. 3. Effects of THC and DPH in mice on the occurrence of tonic hind limb extension induced by s.c. administration of pentylenetetrazol or i.p. injection of strychnine.

even in tests with extremely high doses. THC at low doses did increase latency of the tonic convulsions, as shown in table 1, while DPH also had this effect at a fairly low dose. However, higher doses of DPH (50.0—200.0 mg/kg) significantly decreased the latency below the control value.

Fig. 2 shows that increasing doses of THC and DPH markedly enhanced the lethal effect caused by pentylenetetrazol (85 mg/kg, s.c.) when observed up to 1 hr after administration of this chemoconvulsant. The ED_{50} (±95% confidence limits) was 50.5 mg/kg (24.6—107.0) for THC and 70.5 mg/kg (32.8—151.5) for DPH. However, these agents did not differ significantly from each other in potency for this effect. None of the animals died in groups tested with distilled water or with the vehicle for THC.

The upper portion of fig. 3 shows that a high dose of THC (40 mg/kg) and of DPH (100 mg/kg) both tended to increase the susceptibility to convulsions following various doses of pentylenetetrazol. The ED_{50} for a convulsive effect of pentylenetetrazol was above 60 mg/kg for vehicle-treated, less than 60 mg/kg for THC-treated and less than 30 mg/kg for DPH-treated mice. Combining the two lower doses of pentylenetetrazol (30 and 60 mg/kg), the difference from the vehicle was statistically significant ($\chi^2 = 12.55$, df = 1, $p < 0.001$). The difference between THC and vehicle was much smaller and was not statistically significant.

3.2.5. Effect on strychnine-induced seizures

The third column of numbers in table 1 shows that the convulsant effect of strychnine (3 mg/kg) was counteracted only by PB and CDP. These two compounds at moderately high doses prevented the tonic convulsion and at lower doses increased the latency to this response. Both THC and DPH had no effect on convulsion at the range of doses tested, to a maximum of 80 mg/kg. THC increased latency of the convulsion but only at a very high dose, ED_{50} = 45.0 mg/kg. The lower portion of fig. 3 shows the effects of THC and

DPH on the percentage of animals which convulsed at two lower doses of strychnine in addition to the dose (3.0 mg/kg) used in the study summarized in table 1. It is evident from fig. 3 that both drugs failed to counteract the effect of lower doses of strychnine on convulsion. On the contrary, both drugs tended to increase the percentage of animals convulsing at all 3 doses of strychnine. The difference from vehicle was larger for DPH than for THC but for both drugs it was not statistically significant.

3.2.6. Effect on nicotine-induced seizures

The right-hand column of table 1 summarizes the effects of each of the 4 compounds on seizures induced by nicotine (20 mg/kg). None of the compounds prevented convulsions, but at sufficiently high doses all of them prevented mortality. CDP was the most effective of these drugs, preventing mortality at a moderate dose and increasing latency of convulsion at a fairly low dose. The other 3 compounds, including THC, required very high doses to prevent mortality and fairly high doses, especially in the case of DPH, to increase latency.

4. Discussion

In general, both THC and DPH were relatively effective in counteracting electroconvulsive seizures and ineffective in counteracting chemically induced seizures. These findings are consistent with reports that both THC and DPH decrease polysynaptic transmissions and post-tetanic potentiation (Woodbury and Esplin, 1959; Dagirmanjian and Boyd, 1962; Oskoui, 1971). Woodbury and Esplin (1959) have shown that DPH reduces post-tetanic potentiation within the spinal cord whereas Oskoui (1971) showed this effect with THC at the neuromuscular junction. Therefore, THC and DPH give evidence for anticonvulsant specificity, in contrast to the generalized sedative effects of PB and CDP, which counteract both electrical and chemical convulsant agents.

The several measures of electroconvulsive shock show differential patterns of effects for THC and DPH. With respect to preventing convulsion, DPH was effective at the lowest dose and THC required the highest dose; PB was effective at a lower dose than was CDP. This rank-order of potency agrees with earlier findings on clinical effectiveness in humans against grand mal seizures (Millichap, 1969). With respect to increasing latency and preventing mortality, THC was effective at the lowest dose and DPH was one of the least effective. This is consistent with evidence for general depressant effects of THC (Kubena and Barry, 1970).

Tests at different time intervals indicated that the 0.5 hr interval selected for all the drugs was close to the peak action of THC and was more potent than 2.0 hr for all the drugs except DPH. Previous reports of peak anticonvulsant effects of DPH and PB at 2 or 3 hr were with the slower oral route (Chen et al., 1968; Mitchell and Keasling, 1960; Raines et al., 1973) or s.c. route (Swinyard et al., 1952). The peak effect of CDP has been reported at 0.5 hr with the i.p. route (Chen et al., 1968).

The two vehicles (water and propylene glycol) showed no significant differences by themselves or in combination with any of the drugs in susceptibility to electroconvulsive seizure. Therefore, any effect of the propylene glycol or synergism with the drugs used in this experiment was slight and inconsistent. Zaroslinski et al. (1971) reported that propylene glycol doses up to 8.32 g/kg, much higher than the 1.04 g/kg given in the present experiment, failed to prevent MES.

The finding that both THC and DPH increased susceptibility to convulsion caused by pentylenetetrazol and by strychnine agrees with the earlier findings reported by Loewe and Goodman (1947) for marihuana extract and some synthetic analogs of THC as well as by Mitchell and Keasling (1960) for DPH. THC and DPH are differentiated only in that

THC increased latency of hind limb extension more consistently or at lower doses. The other two compounds, PB and CDP, both effectively inhibited seizures and mortalities caused by pentylenetetrazol and strychnine. These effects of these two drugs confirm the report by Randall (1961).

The nicotine seizures tested in the present experiment produced little differentiation among the drugs but CDP was the only compound which at low doses increased latency of seizure and prevented mortality. Yamamoto et al. (1966) have reported that most drugs including PB were equally effective in protecting mice against nicotine-induced convulsions and death. The dose of nicotine might have been excessively high in the present experiment.

There may be clinical usefulness for a compound such as THC which combines some degree of the anticonvulsant specificity of DPH with the general sedative effect of PB and CDP. Millichap (1969) reported that drugs, such as DPH, which control grand mal tonic seizures in humans are very effective against the MES tonic seizure syndrome in mice and rats. Davis and Ramsey (1949) have demonstrated clinical efficacy of two THC homologs in protecting five institutionalized epileptic children from grand mal seizures.

Acknowledgements

The drug was generously supplied through the courtesy of Monique Braude, Ph.D., Biomedical Research Branch, Division of Research, National Institute on Drug Abuse. The authors gratefully acknowledge the following companies for their generous supply of drugs used in this investigation: Parke-Davis & Company, Detroit, Michigan (DPH sodium), G.D. Searle & Company, Chicago, Illinois (PB sodium) and Hoffman—LaRoche, Inc., Nutley, New Jersey (CDP HCl).

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