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# Anticonvulsant Effects of Cannabinoids in Mice: Drug Interactions within Cannabinoids and Cannabinoid Interactions with Phenytoin

G. B. Chesher and D. M. Jackson

Department of Pharmacology, University of Sydney, N.S.W. 2006, Australia

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*Abstract.* The anticonvulsant activity of orally administered $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), $\Delta^8$-THC, cannabidiol (CBD) and cannabinol (CBN) was tested in mice utilizing electroshock and chemoshock methods. In doses tested $\Delta^9$-THC afforded no protection to mice from chemoshock seizures and was effective against electroshock only in high doses (160—200 mg/kg). CBD and CBN (150—200 mg/kg) were without effect in both tests.

An interaction between cannbinoids was apparent when all three were administered simultaneously (each at 50 mg/kg) because this combination produced a significant reduction in the duration of the hind-limb extensor phase of the electroshock seizures.

The administration of $\Delta^9$-THC significantly potentiated the anticonvulsant effectiveness of phenytoin against electroshock seizures and this effect was further potentiated by the concurrent administration of CBD. Whilst the potentiation of phenytoin by $\Delta^9$-THC (50 mg/kg) was of the order of 1.5 times, the combination of $\Delta$-$^9$THC and CBD (each 50 mg/kg) produced a four-fold potentiation.

Neither within-cannabinoid interaction nor cannabinoid potentiation of phenobarbitone effectiveness could be demonstrated in chemoshock tests.

The mechanism of the cannabinoid facilitation of phenytoin is unknown but it possibly involves activity at central nervous system level rather than being a metabolic interaction. This drug interaction may have potential clinical significance.

*Key words:* $\Delta^9$-Tetrahydrocannabinol — Cannabidiol — Cannabinol — Phenytoin — Phenobarbitone — Anticonvulsant — Drug-Interactions.

## Introduction

Earlier this century the therapeutic use of preparations of cannabis was quite widespread and one condition for which claims of efficacy were made was epilepsy (O'Shaughnessy, 1842; Reynolds, 1890; Davis and Ramsay, 1949). Experimental studies utilizing electroshock seizures in experimental animals also have reported anticonvulsant activity of cannabis extracts, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) or synthetic derivatives of $\Delta^9$-THC (Loewe and Goodman, 1947; Garriott, Forney, Hughes and Richards, 1968; Sofia, Solomon and Barry, 1971; Fujimoto, 1972; Consroe and Man, 1973). Some workers have also reported can-

nabis to have a protective effect against chemoschok (Carlini, Leite, Tannhauser and Berardi, 1973).

The interactions of cannabis derivatives with other drugs as well as interactions between the cannabinoids themselves have recently come under investigation. The prolongation of barbiturate anaesthesia by cannabis extracts, $\Delta^9$-THC and cannabidiol (CBD) has been reported (Loewe, 1944; Gill, Paton and Pertwee, 1970; Garriott *et al.*, 1968; Paton and Pertwee, 1972; Chesher, Jackson and Starmer, 1974; Kubena and Barry, 1970). Interactions between $\Delta^9$-THC and CBD and $\Delta^9$-THC and CBN on the duration of barbiturate anaesthesia (Krantz, Berger and Welch, 1971; Chesher *et al.*, 1974), and between CBD and $\Delta^9$-THC on intestinal motility (Anderson, Jackson and Chesher, 1974) have been demonstrated.

In the present paper we report the results of an investigation of the effects of $\Delta^9$-THC, CBN and CBD on electroshock and chemoshock induced convulsions in mice and of the interactions of cannabinoids with the anticonvulsants, phenytoin and phenobarbitone.

## Methods

Random bred QS strain male mice (20—35 g) were used. In one experiment, C57 inbred strain male mice were used to determine the possibility of response variation due to strain difference. Animals were allowed food and water *ad libitium* up to the time of experimentation. $\Delta^8$-THC and $\Delta^9$-THC were dissolved or suspended in propylene glycol and stored at −20°C. Immediately prior to the experiment the compounds were diluted with lissapol-dispersol solution (I.C.I.; Whittle, 1964) to produce a final concentration of 5% or 10% propylene glycol. CBN and CBD were prepared in 5% or 10% propylene glycol in lissapol-dispersol on the day of the experiment. Where a vehicle control was administered, the appropriate concentration of propylene glycol in lissapol-dispersol was used. However, in no case was any difference observed between the responses of animals treated with either vehicle.

Except where otherwise mentioned, cannabinoids and vehicle controls were administered by gavage. Sodium phenytoin, sodium phenobarbitone were dissolved in 0.9% saline and administered by intraperitoneal (ip) injection. All drugs were given in a dose volume of 1 ml/100 g body weight, unless otherwise stated. All experiments were conducted in a blind manner so that the experimenter was not aware of the identity of each dose-group. Results were analysed either by simple (one way) analysis of variance (Snedecor and Cochran, 1967) or students' *t*-test and dose-response curves by the method of Litchfield and Wilcoxon (1949).

*Chemoshock Methods.* Convulsions were induced by a continuous, slow intravenous injection of a solution of pentylenetatrazol (PTZ), 6 mg/ml in 0.9% saline, using a Thorp-Palmer constant injection apparatus, linked to a Philips timer both of which were operated by a single foot-switch. The solution injected at a rate of 0.318 ml/min (equivalent to 1.9 mg/min), produced clonic convulsions in all mice tested within 20—30 sec, and the dosage required (mg/kg) was calculated for each animal.

Cannabinoids or vehicle control were administered 0.5 h prior to the PTZ. Interactions of $\Delta^9$-THC or CBD with the anticonvulsant phenobarbitone were in-

vestigated by administering the cannabinoids 15 min before phenobarbitone administered ip and 30 min before the intravenous PTZ.

*Electroshock Methods.* The procedure used was that of Swinyard (1949) and Swinyard, Brown and Goodman (1952). Maximal electroshock seizure (MES) was induced using a current of 50 mA, 50 Hz and 0.3 sec duration applied by corneal electrodes moistened with 0.9% saline. Responses were recorded as (a) the abolition of the hind-limb extensor component of the MES and (b) the duration of the hind-limb extensor phase. To ensure that onset of activity was not missed, the MES test was repeated at hourly intervals to 4 h after administration of cannabinoids. Repeated shocking of mice in this manner has been shown by Brown (1952) and by Swinyard *et al.* (1952) to have no significant effect upon the pattern or duration of the hind-limb extensor phase of the electrically induced seizures.

For studies of the interaction between phenytoin (administered ip) and the cannabinoids, $\Delta^9$-THC and CBD (each 50 mg/kg, by gavage), mice were dosed 2 h before testing. Doses of phenytoin were between 2 and 14.9 mg/kg depending on the dose of cannabinoid given concurrently. In all cases, at least 6 doses were used for each dose-response curve and between 15 to 20 animals used at each dose level.

## Results

*Chemoshock Studies.* $\Delta^9$-THC (1—80 mg/kg), CBD and CBN (150mg/kg) were all ineffective in protecting QS mice against PTZ induced convulsions. In various experiments, control animals required between $30.0 \pm 1.4$ ($\pm$ S.E.M.) ($n = 16$) and $37.7 \pm 1.0$ ($\pm$ S.E.M.) ($n = 18$) mg PTZ/kg to produce convulsions. Phenobarbitone was effective in raising the convulsive threshold in a dose-dependent manner (Table 1), whilst phenytoin, in a dose which was effective in electroshock induced convulsions (15 mg/kg), was inactive. The administration of $\Delta^9$-THC or CBD, 50 or 100 mg/kg, 15 min before phenobarbitone, (5, 15 or 25 mg/kg) did not affect the total dose of PTZ necessary to induce convulsions.

*Electroshock Studies.* Table 2 summarizes effects of premedication with $\Delta^8$-THC (25—100 mg/kg), CBD (50—200 mg/kg), or CBN (50—200 mg/kg), none of which was able to abolish the hind limb extensor phase of the electroshock seizures. $\Delta^9$-THC, at 10, 20, 40, 80, 160 and 200 mg/kg, in a total of 100 QS mice, protected only 11 animals from electroshock convulsions. However five of these animals (at dosage groups 40 and 80 mg/kg) were protected at only one of the hourly test periods and this response may have been due to a faulty placement of the electrodes. Only at 160 and 200 mg $\Delta^9$-THC/kg were animals protected at each of the testing periods. This occurred in 2 out of 10 mice at 160mg/kg, and in 4 out of 10 mice at 200 mg/kg. On this basis the $ED_{50}$ of $\Delta^9$-THC for protection against convulsions after oral administration appears to be greater than 200 mg/kg.

Using as end point the duration of hind limb extensor phase and analysing the results for all four time intervals by simple (one way) analysis of variance, a significant effect was observed in the groups which received 40, 160 and 200 mg $\Delta^9$-THC/kg and 100 mg $\Delta^8$-THC/kg. The

Table 1. The effect of phenobarbitone (PB), $\Delta^9$-THC and CBD against PTZ$^{++}$ induced convulsions in QS male mice (For details see methods and results)

| Drug and Dose (mg/kg) | Mean dose (mg/kg) of PTZ$^{++}$ required to produce convulsions $\pm$ S.E.M.* ($n$) |
|---|---|
| a) | |
| Control | 30.2 $\pm$ 2.0 (16) |
| THC (1) | 33.3 $\pm$ 0.9 (16) |
| THC (10) | 28.7 $\pm$ 1.3 (16) |
| THC (20) | 28.5 $\pm$ 1.3 (15) |
| THC (40) | 28.8 $\pm$ 1.0 (16) |
| THC (80) | 27.8 $\pm$ 1.3 (16) |
| Control | 37.7 $\pm$ 1.0 (18) |
| CBD (150) | 39.8 $\pm$ 1.3 (19) |
| CBN (150) | 39.3 $\pm$ 1.6 (18) |
| b) | |
| Control (first) | 30.0 $\pm$ 1.4 (16) |
| Control (second) | 31.2 $\pm$ 0.8 (20) |
| Control (third) | 31.5 $\pm$ 1.0 (20) |
| PB (5) | 38.8 $\pm$ 1.3 (20) |
| PB (15) | 49.6 $\pm$ 2.0 (20) |
| PB (25) | 56.1 $\pm$ 1.7 (14) |
| PB (25) + THC (50) | 56.1 $\pm$ 2.3 (23) |
| PB (25) + THC (100) | 54.5 $\pm$ 2.2 (20) |
| PB (5) + CBD (50) | 40.6 $\pm$ 1.3 (20) |
| PB (15) + CBD (50) | 50.7 $\pm$ 1.3 (20) |

* S.E.M. = standard error of the mean, $n$ = number of animals.
$^{++}$ PTZ = pentylenetetrazol.

dose group which received 80 mg $\Delta^9$-THC/kg was not significantly different from controls in this test. These results are expressed in Table 2, where it will also be noted that the dose of 20 mg $\Delta^9$-THC/kg and of 75 mg $\Delta^8$-THC/kg significantly lengthened rather than shortened the hind limb extensor time when tested 1 h after administration.

To examine the effect of route of administration, three groups each of 20 mice received either vehicle control, 10 or 20 mg $\Delta^9$-THC/kg intravenously (iv) and were tested by electroshock at 0.5 and 1 h after dosing. At 0.5 h the respective mean extensor times ($\pm$ S.E.M.) for the control, 10 and 20 mg $\Delta^9$-THC/kg groups were 12.8 $\pm$ 0.4 sec, 12.1 $\pm$ 1.4 and 7.4 $\pm$ 1.2. Only the 20 mg $\Delta^9$-THC/kg dosage level afforded significant protection. When tested 1 h after dosage the mean extensor times were 18.0 $\pm$ 0.9, 12.1 $\pm$ 1.3 and 11.1 $\pm$ 0.9 suggesting that both 10 and 20 mg $\Delta^9$-THC/kg afford protection. However, although the extensor time was shortened, all mice in all dosage groups convulsed.

Table 2. Effect of premedication with $\Delta^8$-THC, $\Delta^9$-THC, CBD and CBN (and various mixtures of these drugs) on electroshock induced convulsions 1, 2, 3 and/or 4 h after administration in QS mice. The data are expressed as the mean hind limb extensor time (sec) ± S.E.M.

| Drug and Dose** (mg/kg) | Time of testing after administration (h) | | | | $n$++ | + |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | | |
| $\Delta^8$-THC (25) | 16.0 ± 0.4 | 19.6 ± 0.8 | 20.0 ± 0.8 | 19.6 ± 1.4 | 10 | a |
| (50) | 15.7 ± 1.8 | 18.0 ± 1.3 | 18.6 ± 1.5 | 17.6 ± 0.9 | 10 | b |
| (75) | 18.3 ± 0.7[1] | 18.8 ± 1.4 | 18.8 ± 1.8 | 19.4 ± 1.3 | 10 | c |
| (100) | 15.4 ± 0.8 | 15.7 ± 1.7 | 14.8 ± 2.2 | 14.9 ± 2.4 | 10 | d |
| Control | 15.2 ± 0.7 | 19.0 ± 0.7 | 18.0 ± 1.1 | 18.3 ± 1.6 | 10 | e |
| $\Delta^9$-THC (10) | 16.8 ± 0.5 | 18.6 ± 0.8 | 17.3 ± 0.9 | 17.6 ± 0.9 | 10 | f |
| (20) | 18.9 ± 1.1[2] | 19.4 ± 1.0 | 19.6 ± 1.8 | 19.5 ± 1.3 | 10 | g |
| Control | 14.6 ± 0.5 | 17.1 ± 1.0 | 18.9 ± 0.9 | 17.9 ± 1.1 | 10 | h |
| $\Delta^9$-THC (40) | 16.1 ± 0.5 | 18.2 ± 1.1 | 16.3 ± 0.8 | 15.8 ± 0.7 | 10 | i |
| (80) | 15.3 ± 0.8 | 16.0 ± 1.4 | 15.9 ± 1.4 | 14.6 ± 0.6 | 10 | j |
| Control | 14.4 ± 1.0 | 16.4 ± 1.6 | 15.7 ± 1.6 | 14.1 ± 1.9 | 10 | k |
| $\Delta^9$-THC (160)* | 10.1 ± 2.3 | 11.1 ± 1.4[3] | 10.1 ± 1.9[4] | 11.2 ± 1.7 | 10 | |
| (200)* | 10.2 ± 2.9 | 13.0 ± 3.2 | 12.4 ± 2.6 | 12.4 ± 2.4 | 10 | |
| Control * | 14.1 ± 0.5 | 16.9 ± 1.0 | 16.3 ± 1.0 | 15.4 ± 1.2 | 10 | |
| CBD (50) | | 16.4 ± 0.6 | | | 20 | |
| (100) | | 17.3 ± 0.7 | | | 20 | |
| (200)* | | 15.0 ± 0.7 | | | 20 | |
| CBN (50) | | 17.7 ± 0.8 | | | 20 | |
| (100) | | 17.9 ± 0.6 | | | 20 | |
| (200)* | | 16.8 ± 0.6 | | | 20 | |
| Control 1 | | 17.0 ± 0.5 | | | 20 | |
| Control 2* | | 16.9 ± 0.6 | | | 20 | |
| CBN + CBD (50 + 50) | | 14.9 ± 0.6 | | | 20 | |
| CBN + $\Delta^9$-THC (50 + 50) | | 14.6 ± 1.5 | | | 20 | |
| CBD + $\Delta^9$-THC (50 + 50) | | 11.1 ± 2.1 | | | 20 | |
| $\Delta^9$-THC + CBD + CBN (50 + 50 + 50) | | 11.0 ± 1.5[5] | | | 20 | |
| Control | | 15.3 ± 0.7 | | | 20 | |

[1] $t = 3.1$ $P < 0.01$; [2] $t = 3.0$ $P < 0.01$; [3] $t = 3.37$ $P < 0.005$; [4] $t = 2.88$ $P < 0.01$; [5] $t = 2.59$ $P < 0.02$. In these $t$-tests, the value is compared to the appropriate control. ** The vehicle in all cases was 5% propylene glycol except where marked *, which are 10%. ++ number of animals. + One way analysis of variance; the following pairs are significant: ik, $F = 55.09$, $P < 0.01$; jk, $F = 17.99$, $P < 0.01$; fh, $F = 3.57$, $P < 0.05$; de, $F = 7.9$, $P < 0.05$.

*Cannabinoid-Interactions.* Groups of 20 mice were given CBD or CBN, 50, 100 and 200 mg/kg 2 h before electroshock. All mice convulsed and there was no significant effect on the duration of the mean tonic extensor phase of the seizures. However, when the cannabinoids were administered together using doses of 50 mg/kg of each $\Delta^9$-THC, CBD and CBN a significant ($P < 0.02$ anticonvulsant effect was produced (Table 2). The combination of $\Delta^9$-THC and CBD although reducing the mean duration of the extensor phase from that of the control, failed to reach significance ($t = 1.90$; $0.1 > P > 0.05$).

*Interaction of Cannabinoids with Phenytoin.* Phenytoin, administered ip in various doses to groups of 15 to 20 mice 2 h before testing afforded dose-dependent protection against electroshock seizures (see Table 3). When a constant dose of 50 mg $\Delta^9$-THC/kg was given by gavage immediately before phenytoin, a significant reduction in the $ED_{50}$ for phenytoin was produced. The reduction in phenytoin $ED_{50}$ was apparent both when results were assessed as number of mice protected from seizures as well as the duration of extensor time. The phenytoin dose-response curves, with and without $\Delta^9$-THC were all parallel.

50 mg CBD/kg, when tested with phenytoin under the same conditions as described above for $\Delta^9$-THC, also significantly potentiated the anticonvulsant effectiveness of phenytoin when results were assessed as number of animals protected from electroshock seizures ($P < 0.05$). When mice received both CBD and $\Delta^9$-THC, each at 50 mg/kg immediately before phenytoin, a marked potentiation in the $ED_{50}$ for phenytion was

Table 3. The interaction between $\Delta^9$-THC or CBD (2 h premedication, 50 mg/kg) administered by gavage and phenytoin (various doses administered intraperitoneally) on electroshock induced convulsions. The data are expressed as the $ED_{50}$ values for phenytoin as calculated by the method of Litchfield and Wilcoxon (1949) either using the dose required to protect 50% of animals against clonic convulsions or that required to reduce the mean extensor time by half. The doses of phenytoin used were between 2 and 14.9 mg/kg depending on the pretreatment, but in every case at least six doses were used. For each point between 15 and 20 animals were used. The data in brackets are the 95% confidence limits of the $ED_{50}$

| Treatment | $ED_{50}$ value (mg/kg) | |
|---|---|---|
| | Clonic convulsions[a] | Extensor time[a] |
| Phenytoin | 11.4 (10.4 — 12.5)[1] | 10.0 (9.1 — 11.0)[5] |
| Phenytoin + $\Delta^9$-THC | 7.3 (6.1 — 8.7)[2] | 6.8 (5.9 — 7.8)[6] |
| Phenytoin + CBD | 9.5 (8.5 — 10.6)[3] | 8.4 (6.9 — 10.2)[7] |
| Phenytoin + CBD + $\Delta^9$-THC | 2.8 (2.3 — 3.4)[4] | 2.6 (2.2 — 3.0)[8] |

1,2; 1,3; 1,4 $P < 0.05$; 5,6; 5,8 $P < 0.05$.

[a] The four curves are parallel.

observed, which was greater (approx 2.5 times) than the potentiation of phenytoin by $\Delta^9$-THC alone (Table 3).

To examine the possibility of a strain insensitivity to cannabinoids of the mice used in these experiments (QS) the effect of $\Delta^9$-THC was studied in a group of mice of the C57 strain. 2 h prior to electroshock a group of C57 male mice were dosed with 100 mg $\Delta^9$-THC/kg or with vehicle as control. All mice convulsed and there was no significant difference in the mean duration of the hind limb extensor phase between dosed and control groups (18.8 $\pm$ 0.9 and 20.1 $\pm$ 1.1 respectively).

However, 12 of the 20 mice (60%) in the control group died within 30 sec after the electroshock whilst all of the treated animals survived. This mortality compared to a total of 13.6% in all cannabinoid treated QS strain mice (340 animals) suggests a greater lethality rate to electroshock in C57 mice. Cannabinoid pretreatment in general afforded almost complete protection against lethality in both strains.

## Discussion

The drugs used in this as standard anticonvulsants, phenobarbitone for chemoshock and phenytoin for electroshock were shown to possess dose-dependent anticonvulsant activity. As expected phenytoin was found to be inactive against PTZ induced convulsions (Swinyard, 1949). The chemoshock procedure used produced minimal PTZ seizures (Consroe and Man, 1973) because at endpoint, clonic convulsions only were produced. The dose of PTZ for all control groups were below the dose of 38 mg/kg i.v. cited by Goodman, Greival, Brown and Swinyard (1953) as being necessary to induce the tonic extensor convulsions. The mean total concentrations of PTZ to induce minimal seizures was not significantly different in mice pre-treated with cannabinoids from that required in the control animals. In these experiments, $\Delta^9$-THC, CBN and CBD in the doses used afforded no protection to mice against the minimal PTZ seizures. These results are in agreement with Loewe and Goodman (1947) and Consroe and Man (1973). In contrast, Sofia *et al.* (1971) found $\Delta^9$-THC to enhance PTZ induced convulsions. Our data do not support this finding although there was a non-significant trend for the $\Delta^9$-THC dosed mice to require a lower mean dose of PTZ to convulse (Table 1).

Protection of mice by cannabis against MES has been demonstrated by a number of authors including Loewe and Goodman (1947) using "natural charas THC" and various homologues; Garriott *et al.* (1968), using THC, synhexyl and other CBN related compounds; Sofia *et al.* (1971) and Fujimoto (1972) both using $\Delta^9$-THC. Most of these authors used as their criterion of protection, a reduction in the mean duration of the tonic extensor phase of the seizure. Fujimoto (1972) however, reported that $\Delta$-$^9$THC, administered iv was able to abolish the tonic limb

extensor phase with and $ED_{50}$ of approx 0.5 mg/kg. In our hands, neither oral $\Delta^8$-THC in doses up to 100 mg/kg nor $\Delta^9$-THC up to 160 mg/kg abolished the tonic limb extension, though at 200 mg $\Delta^9$-THC/kg some animals were protected. Our estimated $ED_{50}$ for orally administered $\Delta^9$-THC for abolition of tonic convulsions would be in excess of 200 mg/kg. In doses of 10 and 20 mg $\Delta^9$-THC/kg iv we were unable to protect animals from convulsions although there was a significant reduction in the duration of the tonic extensor phase at the higher dose. Our studies did not appear to involve an animal strain difference as similar results were obtained using two strains of mice.

These results do not suggest that $\Delta^9$-THC possesses significant anticonvulsant activity especially when compared with the clinically useful drugs, phenobarbitone and phenytoin. Furthermore we agree with Sofia *et al.* (1971) and Loewe and Goodman (1947) that the $\Delta^9$-THC spectrum of activity more closely resembles that of phenytoin than that of phenobarbitone. Similarly, we found that CBD and CBN were ineffective in protecting animals from either chemoshock (150 mg/kg) or electroshock (doses up to 200 mg/kg).

The most interesting results in our studies were those of the interactions of the cannabinoids, both within themselves and with phenytoin against electroshock seizures (Table 3). Although $\Delta^9$-THC, CBD and CBN each at 50 mg/kg were themselves inactive, when given together they produced a significant reduction in the duration of the tonic extensor convulsions. This result adds another parameter to those already reported of an interaction between cannabinoids (Anderson *et al.*, 1974) when assessed on the activity on gastrointestinal motility and when assessed on the duration of pentobarbitone anaesthesia (Chesher *et al.*, 1974).

The interaction of $\Delta^9$-THC and CBD with phenytoin was particularly noteworthy. CBD or $\Delta^9$-THC in doses which themselves were inactive in our tests significantly potentiated the anticonvulsant effectiveness of phenytoin. This finding confirms an earlier report by Loewe and Godman (1947) that there occurred a "synergism between diphenylhydation and marihuana-active compounds" although no data were presented to support this statement. The mechanism of this interaction is unknown, though one can speculate that it might involve a metabolic interaction presumably in the liver. Other studies in this laboratory involving drug interactions of the cannabinoids on the passage of a charcoal meal in mice suggests that these occur after oral, but not after intravenous administration (Anderson, Jackson and Chesher, unpublished observations). However the absence of a similar interaction between the cannabinoids and phenobarbitone in the PTZ chemoshock studies casts some doubt upon this

hypothesis, although different enzyme systems could presumably be involved. An interaction between barbiturate and cannabinoids especially CBD is now well documented, both *in vivo* (Gill *et al.*, 1970; Kubena and Barry, 1970; Paton and Pertwee, 1972) and *in vitro* (Cohen, Peterson and Mannering, 1971; Paton and Pertwee, 1972; Dingell, Miller, Heath and Klausner, 1973) and it was surprising that cannabinoids did not show a similar interaction with phenobarbitone in these studies. On the other hand, Kubena and Barry (1970), Fujimoto (1972) and Chesher *et al.* (1974) considered that the interaction between barbiturates and $\Delta^9$-THC was, in part at least, at central nervous system level. One can speculate that this possibility may explain the interaction of $\Delta^9$-THC with phenytoin described in the present study. $\Delta^9$-THC failed to show activity either alone or in potentiating the effects of phenobarbitone in the chemoshock studies, whilst it did show some activity against electroshock seizures and also potentiated the activity of phenytoin.

The interaction of cannabinoids with phenytoin may be of clinical significance. It should be possible to find or synthesize a cannabinoid which is devoid of subjective mood altering effects which can potentiate phenytoin. Such a drug combination may alleviate many of the troublesome toxic effects of this drug. Furthermore the possibility of such an interaction occurring in a patient receiving phenytoin and who also is taking marihuana should be considered. Such interactions may lead to an apparent overdosage effect of phenytoin.

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## References

Anderson, P. F., Jackson, D. M., Chesher, G. B.: The interaction of $\Delta^9$-tetrahydrocannabinol and cannabidiol on intestinal motility in mice. J. Pharm. Pharmacol. **26**, 136–137 (1974)

Brown, W. C.: Unpublished observations (1952) cited by Swinyard *et al.* (1952)

Carlini, E. A., Leite, J. R., Tannhauser, M., Berardi, A. C.: Cannabinol and *Cannabis sativa* extract protect mice and rats against convulsive agents. J. Pharm. Pharmacol. **25**, 664–665 (1973)

Chesher, G. B., Jackson, D. M., Starmer, G. A.: Interaction of cannabis and general anaesthetic agents in mice. Brit. J. Pharmacol. (in press) (1974)

Cohen, G. M., Peterson, D. W., Mannering, G. J.: Interactions of $\Delta^9$-tetrahydrocannabinol with the hepatic microsomal drug metabolizing system. Life Sci. **10**, 1207–1215 (1971)

Consroe, P. F., Man, D. P.: Effects of $\Delta^8$- and $\Delta^9$-tetrahydrocannabinol on experimentally induced seizures. Life Sci. **13**, 429–439 (1973)

Davis, J. P., Ramsey, H. H.: Antiepileptic action of marihuana-active substances. Fed. Proc. **8**, 284–285 (1949)

Dingel, J. V., Miller, K. W., Heath, E. C., Klausner, H. A.: The intracellular localization of $\Delta^9$-tetrahydrocannabinol in liver and its effects on drug metabolism *in vitro*. Biochem. Pharmacol. **22**, 949–958 (1973)

Fujimoto, J. M.: Modification of the effects of $\Delta^9$-tetrahydrocannabinol by phenobarbital pretreatment in mice. Toxicol. appl. Pharmacol. **23**, 623–634 (1972)

Garriott, J. C., Forney, R. B., Hughes, F. W., Richards, A. B.: Pharmacologic properties of some cannabis related compounds. Arch. int. Pharmacodyn. **171**, 425–434 (1968)

Gill, E. W., Paton, W. D. M., Pertwee, R. G.: Preliminary experiments on the chemistry and pharmacology of cannabis. Nature (Lond.) **228**, 134–136 (1970)

Goodman, L. S., Greival, M. S., Brown, W. C., Swinyard, E. A.: Comparison of maximal seizures evoked by pentylenetetrazol (Metrazol) and electroshock in mice, and their modification by anticonvulsants. J. Pharmacol. exp. Ther. **108**, 168–176 (1953)

Krantz, J. C., Berger, H. J., Welch, B. L.: Blockade of (–)trans-$\Delta^9$-tetrahydrocannabinol depressant effect by cannabinol in mice. Amer. J. Pharm. **143**, 149–152 (1971)

Kubena, R. K., Barry, H.: Interactions of $\Delta^1$-tetrahydrocannabinol with barbiturates and amphetamines. J. Pharmacol. exp. Ther. **173**, 94–100 (1970)

Litchfield, J. T., Wilcoxon, F.: A simplified method of evaluating dose-effect experiments. J. Pharmacol. exp. Ther. **96**, 99–113 (1949)

Loewe, S.: Studies on the pharmacology of marihuana. In: The marihuana problems in the city of New York. Ed. by the Mayor's Committee on Marihuana, pp. 149–212. Lancaster, Pa.: The Jaques Catell Press 1944

Loewe, S., Goodman, L. S.: Anticonvulsant action of marihuana active substances. Fed. Proc. **6**, 352 (1947)

O'Shaughnessy, W. B.: On the preparations of the Indian hemp or guna (cannabis indica): the effects on the animal system in health and their utility in the treatment of tetanus and other convulsive disorders. Trans. Med. Physiol. Soc. Bombay, p. 460 (1842)

Paton, W. D. M., Pertwee, R. G.: Effect of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. Brit. J. Pharmacol. **44**, 250–261 (1972)

Reynolds, J. R.: Therapeutical uses and toxic effects of cannabis indica. Lancet **1**, 637–638 (1890)

Sofia, R. D., Solomon, T. A., Barry, H.: The anticonvulsant activity of $\Delta^1$-tetrahydrocannabinol in mice. Pharmacologist **13**, 246 (1971)

Snedecor, G. W., Cochran, W. G.: Statistical methods. Iowa State University Press 1967

Swinyard, E. A.: Laboratory assay of clinically effective antiepileptic drugs. J. Amer. pharm. Ass. **38**, 201–204 (1949)

Swinyard, E. A., Brown, W. C., Goodman, L. S.: Comparative assays of antiepileptic drugs in mice and rats. J. Pharmacol. exp. Ther. **106**, 319–330 (1952)

Whittle, B. A.: The use of changes in capillary permeability in mice to distinguish between narcotic and non-narcotic analgesics. Brit. J. Pharmacol. **22**, 246–253 (1964)

Dr. G. B. Chesher
Department of Pharmacology
The University of Sydney
Sydney, N. S. W. 2006, Australia