REFERENCES

BEN-ZVI, Z. & BURSTEIN, S. (1975). *Biochem. Pharmac.*, **24**, 1130–1131.

BEN-ZVI, Z., MECHOULAM, R. & BURSTEIN, S. (1970). *J. Am. chem. Soc.*, **92**, 3468–3469.

BEN-ZVI, Z., MECHOULAM, R., EDERY, H. & PORATH, G. (1971). *Science*, **174**, 951–952.

BINDER, M., AGURELL, S., LEANDER, K. & LINDGREN, J.-E. (1974). *Helv. chim. Acta*, **57**, 1626–1641.

BLOCK, J. H. & DJERASSI, C. (1973). *Steroids*, **22**, 591–596.

DALY, J. W., JERINA, D. M. & WITKOP, B. (1972). *Experientia*, **28**, 1129–1149.

GURNY, O., MAYNARD, D. E., PITCHER, R. G. & KIERSTEAD, R. W. (1972). *J. Am. chem. Soc.*, **94**, 7928–7929.

HARVEY, D. J., GLAZENER, L., STRATTON, C., JOHNSON, D. B., HILL, R. M., HORNING, E. C. & HORNING, M. G. (1972a). *Res. Commun. Chem. Path. Pharmac.*, **4**, 247–260.

HARVEY, D. J., JOHNSON, D. B. & HORNING, M. G. (1972b). *Analyt. Letters*, **5**, 745–755.

HARVEY, D. J., MARTIN, B. R. & PATON, W. D. M. (1977). *Biomed. Mass Spectrom.* In the press.

HARVEY, D. J. & PATON, W. D. M. (1976a). In: *Marihuana; Chemistry, Biochemistry and Cellular Effects*, pp. 93–109. Editors: G. G. Nahas, W. D. M. Paton & J. E. Idänpään-Heikkilä. New York: Springer.

HARVEY, D. J. & PATON, W. D. M. (1976b). *Res. Commun. Chem. Path. Pharmac.*, **13**, 585–599.

MAYNERT, E. W., FOREMAN, R. L. & WATABE, T. (1970). *J. biol. Chem.*, **245**, 5234–5238.

MCCLOSKEY, J. A., STILLWELL, R. N. & LAWSON, A. M. (1968). *Analyt. Chem.*, **40**, 233–236.

MECHOULAM, R., BEN-ZVI, Z., VARCONI, H. & SAMUELOV, Y. (1973). *Tetrahedron.*, **29**, 1615–1619.

MECHOULAM, R., VARCONI, H., BEN-ZVI, Z., EDERY, H. & GRUNFELD, Y. (1972). *J. Am. chem. Soc.*, **94**, 7930–7931.

OESCH, F., KAUBISCH, N., JERINA, D. M. & DALY, J. W. (1971). *Biochemistry*, **10**, 4858–4866.

SCHMIDT, H., RICHTER, P. & MÜHLSTÄDT, M. (1963). *Chem. Ber.*, **96**, 2636–2643.

WALL, M. E. & BRINE, D. R. (1976). In: *Marihuana; Chemistry, Biochemistry and Cellular Effects*, pp. 51–62. Editors: G. G. Nahas, W. D. M. Paton and J. E. Idänpään-Heikkilä. New York: Springer.

WIDMAN, M., NORDQVIST, M., DOLLERY, C. T. & BRIANT, R. H. (1975). *J. Pharm. Pharmac.*, **27**, 842–848.

Anticonvulsant interaction of cannabidiol and ethosuximide in rats

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Cannabidiol (CBD), a major component of marihuana, has been shown to have dose-response anticonvulsant activity in laboratory animals (Karler, Cely & Turkanis, 1973) and to be devoid of typical marihuana-like psychoactivity in man (Hollister, 1973; Karniol, Shirakawa & others, 1974). Furthermore, CBD is a potent inhibitor of the hepatic microsomal drug-metabolizing enzymes in rodents (Fernandes, Warning & others, 1973). These previous findings and a recent survey showing high incidence of marihuana usage among young epileptics (Feeney, 1976) led us to explore the combined effects of CBD and various standard antiepileptic drugs against electrically- and sound-induced seizures in rats (Consroe & Wolkin, 1977). In the latter study, one anti-epileptic drug, ethosuximide, failed to elicit a graded dose-response effect in either of the two seizure tests. We now report additional data on the interactive effects of CBD and ethosuximide against leptazol-induced minimal (clonic) seizures in rodents. Comparative data are also presented on the interactive effects of ethosuximide, which is extensively metabolized *in vivo* (Chang, Burkett & Glazko, 1972), and an inhibitor of hepatic microsomal enzymes, SKF 525A.

* Correspondence.

CBD was incorporated into a 10% polysorbate (Tween 81) 80–0·9% saline vehicle and ethosuximide, SKF 525A (β-diethylaminoethyldiphenylpropylacetate hydrochloride) and leptazol were dissolved in 0·9% saline. Male Sprague-Dawley rats (200–300 g) were treated in groups of ten with one of the following: Tween 81-saline (2 ml, oral), saline (1 ml, i.p.), ethosuximide (250 mg kg^{-1}, oral), CBD (34 mg kg^{-1}, oral), CBD (17 mg kg^{-1}, i.v.), and SKF 525A (10 mg kg^{-1}, i.p.). Each treatment was followed by leptazol (70 mg kg^{-1}, s.c.) at 1, 2, 4, and 8 h intervals. Of all compounds given, only ethosuximide blocked leptazol-induced minimal seizures and showed a maximum effect at 1 h. A median effective dose (ED50) of ethosuximide against leptazol seizures was then determined by the method of Litchfield & Wilcoxon (1949). Subsequently the ED50 of ethosuximide was determined in different animals 1 h after the drug had been given concurrently with CBD (34 mg kg^{-1}, oral) or SKF 525A (10 mg kg^{-1}, i.p.). Anticonvulsant potency comparisons among ED50 of ethosuximide alone and with the two other agents showed significant differences ($P < 0.05$) of the following order: SKF 525A + ethosuximide > ethosuximide > CBD + ethosuximide. The ED50 and 95% confidence limits (in mg kg^{-1}) were: SKF 525A + ethosuximide,

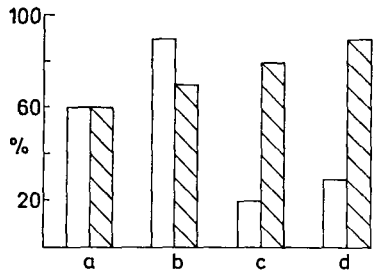

FIG. 1. The anticonvulsant effects of ethosuximide drug interactions against leptazol clonic seizures in rats. Tween-saline vehicle (2 ml, oral), SKF 525A (10 mg kg^{-1}, i.p.) or cannabidiol (CBD; 34 mg kg^{-1}, oral or 17 mg kg^{-1}, i.v.) was given concurrently with (open columns) or 1 h before (hatched columns) ethosuximide (250 mg kg^{-1}, oral); leptazol (70 mg kg^{-1}, s.c.) was given 1 h after ethosuximide. Each bar represents effects in 10 rats. Ordinate—% protection against leptazol seizures. a—ethosuximide + Tween-saline, b—ethosuximide + SKF 525A, c—ethosuximide + CBD (oral), d—ethosuximide + CBD (i.v.).

180 (163·6–198·0); ethosuximide, 230 (203·5–259·9); and CBD + ethosuximide, 360 (314·4–412·2). These data indicate that concurrent SKF 525A enhanced and CBD reduced the anticonvulsant potency of ethosuximide.

Additionally, CBD (34 mg kg^{-1}, oral) or SKF 525A (10 mg kg^{-1}, i.p.) was given 1 h before ethosuximide (250 mg kg^{-1}, oral), and CBD (17 mg kg^{-1}, i.v.) was given either 1 h before or with ethosuximide. In each case, leptazol (70 mg kg^{-1}, s.c.) was given 1 h after ethosuximide. Fig. 1 shows the comparisons of anticonvulsant effects of the drug combinations in the pretreatment conditions and when given together. Compared with the effects of the ethosuximide + Tween-saline conditions, there are marked differences in seizure protection with ethosuximide + SKF 525A and ethosuximide + CBD treatments.

SKF 525A, when given concurrently with ethosuximide or as a pretreatment, potentiated the latter's anticonvulsant effects since it undergoes extensive aliphatic side chain oxidation (Chang & others, 1972). This type of reaction is typically inhibited by SKF 525A in the liver (Anders, Alvares & Mannering, 1966). The potentiation observed appears to be a result of the inhibiting effect of SKF 525A on the metabolism of ethosuximide. As both CBD (Fernandes & others, 1973) and SKF 525A (Anders & others, 1966) produce the same type 1 spectral changes of rat liver microsomal inhibition, one might expect CBD to also potentiate the effects of ethosuximide. Anticonvulsant potentiation of this drug was observed in the CBD pretreated groups suggesting a mechanism in hepatic microsomal enzymes. But, concurrent administration with CBD greatly reduced the anticonvulsant potency of ethosuximide. Coldwell, Bailey & others (1974) using a 30 min pretreatment of CBD (i.p.) with pentobarbitone (oral), found the time required to reach peak blood concentrations of pentobarbitone was lengthened compared with that of pentobarbitone alone; this was explained as an inhibitory action of CBD on pentobarbitone absorption. In the present study, oral or intravenous CBD given concurrently with ethosuximide orally, reduced the anticonvulsant activity of the latter drug suggesting that this interaction may not be wholly explained by CBD's action on the liver or gastrointestinal system. Collaterally, ethosuximide is not significantly bound to plasma protein (Chang & others, 1972), theoretically eliminating competition for the lipoprotein binding sites with CBD. We feel further investigation involving central mechanisms may elucidate the cause of this acute antagonism to ethosuximide.

This work was supported by grant DA 01448 from the National Institute on Drug Abuse (NIDA) of the Alcohol, Drug Abuse, and Mental Health Administration. Ethosuximide was kindly donated by Parke-Davis Company and cannabidiol was provided by NIDA.

January 26, 1977

REFERENCES

ANDERS, M. W., ALVARES, A. P. & MANNERING, G. J. (1966). *Mol. Pharmac.*, **2**, 328–337.

CHANG, T., BURKETT, A. R. & GLAZKO, A. J. (1972). In: *Antiepileptic Drugs*, pp. 425–429. Editors: Woodbury, D. M., Penry, J. K., and Schmidt, R. P. New York: Raven Press.

COLDWELL, B. B., BAILEY, K., PAUL, C. J. & ANDERSON, G. (1974). *Toxic. appl. pharmac.*, **29**, 59–69.

CONSROE, P. & WOLKIN, A. (1977). *J. Pharmac. exp. Ther.*, **201**, in the press.

FEENEY, D. M. (1976). *J. Am. Med. Ass.*, **235**, 1105.

FERNANDES, M., WARNING, N., CHRIST, W. & HILL, R. (1973). *Biochem. Pharmac.*, **22**, 2981–2989.

HOLLISTER, L. E. (1973). *Experientia*, **29**, 825–826.

KARLER, R., CELY, W. & TURKANIS, S. A. (1973). *Life Sci.*, **13**, 1527–1531.

KARNIOL, I. G., SHIRAKAWA, I., KASUNSKI, N., PFEFERMAN, A. & CARLINI, E. A. (1974). *Eur. J. Pharmac.*, **28**, 172–177.

LITCHFIELD, J. T. & WILCOXON, F. (1949). *J. Pharmac. exp. Ther.*, **96**, 99–133.