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Combined Effect of Methaqualone and Two Cannabinoids

The purpose of this study was to determine the effect of pretreatment with cannabidiol (CBD) or Δ-9-tetrahydrocannabinol (THC) on methaqualone (MQ)-induced sleeping times. The duration of sleep was determined as the interval between the loss of righting reflex and its return. Male albino mice were injected intraperitoneally (i.p.) with either CBD or THC (10, 20, or 30 mg/kg) or vehicle. Thirty minutes later, an hypnotic dose of MQ (75 mg/kg) was administered. Animals receiving CBD or THC alone would not sleep. The sleeping time for MQ alone was approximately 30 minutes. In the presence of CBD or THC, MQ sleeping times increased significantly. The effect of THC was significantly greater than that of CBD.

Introduction

The sedative hypnotic drug methaqualone was introduced to the American market in 1965. It has the chemical formula 2-methyl-3-0-tolyl-4(3H)-quinazolinone (Fig. 1). After

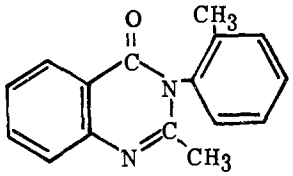

FIG. 1—*Chemical formula of methaqualone.*

intravenous administration in mice, it is concentrated in fat, liver, and, to a lesser extent, brain [*1*]. Once thought to be nonaddicting and to have all the advantages of the barbiturates without the likelihood of high abuse and addiction potential, it was used extensively as a therapeutic agent. The drug's reputation for giving an exceptionally pleasant "high," the belief that it did not create dependence, and street folklore attributing aphrodisiac qualities to methaqualone all contributed to its misuse [*2*]. In 1973, it was placed under Schedule II of the Controlled Substances Act of 1970. Methaqualone

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is popular among college adults [2,3]. Since marihuana use is also common to this group, it could be assumed that these two drugs are sometimes used in combination.

This study was undertaken to examine the effects of pretreatment with two major marihuanna constituents, Δ-9-tetrahydrocannabinol and cannabidiol on methaqualone-induced sleep times in mice (Fig. 2).

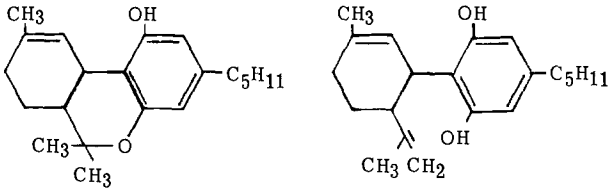

FIG. 2—*Chemical formulas of* (left) *Δ9-tetrahydrocannabinol and* (right) *cannabidiol.*

Materials and Methods

Male Swiss-Webster mice, weighing between 20 and 25 g, were used. All drugs were administered i.p.

The methaqualone (Parke-Davis, Ann Arbor, Mich.) hypnotic dose, 75 mg/kg, was prepared as a suspension in 4% Tween 80® at the beginning of each experimental session so that each animal received 0.2 ml/20 g.

The estimated average lethal dose (LD_{50}) for methaqualone in this vehicle was found to be 281 mg/kg i.p. (range, 265–297).

The drugs used for pretreatment, CBD and Δ-9-THC, were prepared using the method of Brown et al [4]. The compounds were dissolved in a small amount of ethanol and physiological phosphate. Ethanol was removed by steam distillation. Gas chromatography [5] was used to verify that the suspension was ethanol free. The THC or CBD content was determined with a Hewlett Packard Model 402 high efficiency gas chromatograph equipped with a 6 ft by ¼ in. (1.8 m by 6.35 mm) outside diameter glass column packed with a 10% OV 17 stationary phase on chromosorb W, acid washed, 80 to 100 mesh. Imipramine was the internal standard. The temperature of the injection port was 330°C, that of the oven 280°C, and that of the detector 320°C. Flow rates were O_2, 300 ml/min; H_2, 30 ml/min; and N_2, 60 ml/min. The suspension was adjusted to the proper concentration with physiological phosphate. The volume of i.p. injection was 0.5 ml for a 20-g mouse.

Each animal received two injections. The first was either 10, 20, or 30 mg/kg CBD or THC. The control groups received physiological phosphate alone. This was followed after 30 min by methaqualone, 75 mg/kg. The measurement of sleep time began when the animals could no longer right themselves if placed on their backs and ended when the animals were able to turn over from their backs to a normal position three times in a period of 30 seconds. All experiments were started at the same time each day. Mean sleep times for each group were calculated and statistical comparisons between groups were made using repeated *t* tests.

Results

The first study dealt with the effects of CBD pretreatment on methaqualone sleep times (Fig. 3). Four groups of 10 animals each were used. Each group received either physiological phosphate alone or 10, 20, or 30 mg/kg of CBD. The 20 and 30 mg/kg CBD pretreated groups slept significantly longer than did the control group.

Four groups of ten animals each were pretreated with either physiological phosphate or 10, 20, or 30 mg/kg of THC. The THC pretreated groups slept significantly longer at all dose levels than did the control group (Fig. 4).

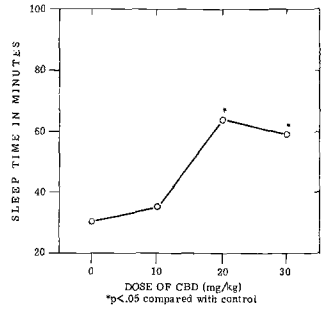

FIG. 3—*Effect of CBD pretreatment on methaqualone sleep.*

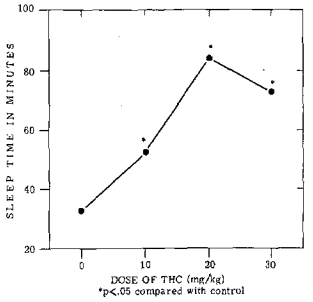

FIG. 4—*Effect of THC pretreatment on methaqualone sleep (75 mg/kg).*

A significantly greater increase in sleep time was produced by THC than by CBD at all dosage levels (Fig. 5). The control groups were not significantly different from each other.

Pretreatment with a mixture containing 20 mg/kg THC plus 20 mg/kg CBD produced a sleep time over control that was slightly more than twofold that of THC alone and nearly threefold that of CBD alone. In the case of both CBD and THC, the highest pretreatment dose given (30 mg/kg) produced a sleep time duration that was not significantly different ($p < 0.05$) from that of the 20 mg/kg pretreatment dose.

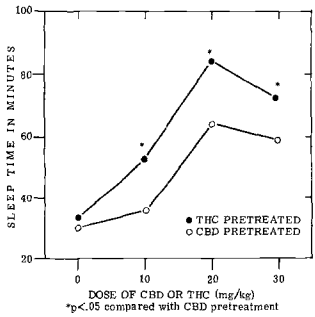

FIG. 5—*Comparison of CBD and THC pretreatment on methaqualone sleep (75 mg/kg).*

Discussion

The three drugs used in this study are all known to be metabolized by liver microsomal enzymes [*6,7*]. The data seems to indicate that there may be competition for this system resulting in longer sleep times in the pretreated animals. It has been demonstrated that CBD is a stronger inhibitor of the cytochrome P450 system than is THC [*7*]. However, THC, unlike CBD, is known to have central effects which may account for the longer sleep times [*8*]. It would seem, also, from the data using the CBD-THC mixture that THC and CBD together are interacting in some way to

enhance methaqualone-induced sleep. The absence of an increased sleep time from 20 to 30 mg/kg in both the CBD and THC pretreated groups suggest a plateau effect, perhaps the result of receptor site saturation.

Pretreatment with these agents may be causing changes in the absorption, distribution, or excretion of the drug as well as in its metabolism.

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