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(—)Δ^9 THC as an Hypnotic

An Experimental Study of Three Dose Levels

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Abstract, (-)A@ THC was found to significantly decrease the time it takes to fall asleep in physically healthy insomniacs. Once asleep, interruptions of sleep were not significantly altered over the whole night. The (—)Δ^9 THC tended to be associated with some decrease in awakenings in the first half of the night.

The primary side effect experienced by the subjects at all dose levels in the Pre-Sleep phase was temporal disorganization and mood alterations. There was an increase in intensity of side effects and number of subjects affected with increasing dosage.

The most significant side effect, however, was a "hangover" phenomenon, or continued 'high" the next day, with some residual of temporal disorganization. It increased in intensity and duration with increase in dosage. This "hangover" seems severe enough to eliminate the consideration of the 30 mg dose range of (—)Δ^9 THC for clinical use as an hypnotic.

Key words: THC — Tetrahydrocannabinol — Hypnotics — Sleep-Induction.

Introduction

Tetrahydrocannabinol [(—)Δ^9 THC], considered by some to be the active ingredient of marijuana, is a controversial psychopharmacologic drug. There are, however, several important qualities about it which are not controversial. The first is its sedative effects which have been mentioned by several authors. The second is that at dose ranges generally used by these authors, there is minimal toxicity. A critical advantage of THC is that even with marked overdose, there has rarely been reported lethality; in this regard it has marked safety advantages over most presently used hypnotics. This sedative quality, plus its minimal toxicity, suggested the possible clinical use of (—)Δ^9 THC as a possible sleep medication.

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The most significant physiologic changes produced by $(-)\Delta^9$ THC are an increase in pulse and an occasional transitory hypotension [1,2,3] which have led some clinical investigators to consider it as a potential anti-hypertensive agent. Other cardiac or respiratory affects have not been noted. No alterations of glucose, lipid, or catecholamine metabolism have been noted [4]. Although temporal disintegration and depersonalization and psychotic-like phenomenon have been reported, these have been transitory and occurred only at high doses [5]. Within the usual range of doses tested, open psychotic breaks, or severe extended neurotic reactions have not been reported.

Preliminary studies using smoked marijuana on sleep EEG, reported by Kales et *al.* [6], showed that the "initial smoking produces a decrease in REM sleep, but very quickly there is a return to REM sleep baseline levels and above baseline levels as the smoking is continued over a short period. "

Objectives. The aims of this study were to examine the hypnotic properties of $(-)\Delta^9$ THC-its efficacy in inducing and maintaining sleep in insomniacs-and to explore the hypnotic/side effect ratio of various doses.

Experimental Procedure

General Design. The general design of the experiment required that nine subjects be tested once a week for a six-week period to determine the effects of $(-)\Delta^9$ THC in altering usual sleep patterns. The first two trials were adjustment trials to the sleep ward in the hospital. The results reported herein came from the last four trials in which subjects were given 10 mg, 20 mg, 30 mg of $(-)\Delta^9$ THC, and a placebo. The $(-)\Delta^9$ THC and placebo were given in a liquid form, The study was double-blind. The only person who knew the drug code was the doctor who prepared the drink and was present until the subjects ingested it. He then withdrew from the sleep laboratory but was on call if needed.

Subject Selection was initiated through a local paper with the advertising for male subjects between the ages of 21-40, with sleep difficulties, to participate in a study with a new (non FDA approved) potential sleep medication. No mention of $(-)\Delta^9$ THC was made.

On initial phone contact, volunteers were told that THC was the drug to be tested. If they had either no prior experience with, or extensive present usage of, marijuana they were excluded from the study. Subjects filled out a questionnaire about their sleep habits; The Langer Psychiatric Impairment Scale, and the Taylor Manifest Anxiety Test. Based on results from these screening materials, nine male candidates

were selected who reported mild insomnia (60—90 min latency in falling asleep), who scored four or less on the Langer Psychiatric Impairment Scale, and who scored less than 20 on the Taylor Manifest Anxiety Test (the average was 15). These candidates were then interviewed by a psychiatrist to further screen out those with any psychotic symptoms or manifestly neurotic individuals. The subjects who passed this screening then went through a physical examination, medical history, and a multiphasic blood screening test.

Setting. The study location was a separate ward in Boston State Hospital where nine beds were set up with dividers between beds. There was also a conference room where subjects could study or read after receiving the medication until they decided to enter the large ward to go to sleep.

Drugs and Dosage. THC was (−)-trans-Δ-9-tetrahydrocannabinol 95% in dehydrated alcohol. It was prepared and obtained from NIMH. It was stored under refrigerated conditions. The taste of the (−)Δ^9THC was masked by placing it in a drink composed of Fresca, bitter lemon, cherry juice and a few drops of almond extract. The placebo was simply these components minus the (−)Δ^9 THC. No subject was able to distinguish the placebo from (−)Δ^9 THC on immediate ingesting of the drink. The three dose levels of THC used were 10, 20, and 30 mg. These dosages spanned a range that has been noted to induce sleep and have some psychoactive effects yet not cause the subjects to lose contact with reality [1,3,5,7]. Each subject received each dose of the (−)Δ^9 THC and a placebo. The sequence of their administration was in accordance with an incomplete Latin square design.

Subjects were instructed not to take any psychoactive drugs for a week before the study began and throughout the study. They were also told not eat for three or 4 hrs before coming to the study site or after receiving the THC. The subjects received the THC or placebo on the study site an hour and a half before the average sleep time of the group. They were encouraged to study, read, or watch T.V. until ready to go to bed. The subjects were allowed moderate but restricted socializing for the first hour after receiving the medication.

***Data** Collection.* An experienced sleep observer-rater was present from the time of drug ingestion until the next morning. He observed and made notations on the subjects every 15 min throughout the night. He was responsible for noting when the subjects went to bed, fell asleep, and if and when they awoke during the night.

In the morning, within one half hour of awakening, questions pertaining to the quality of sleep were asked of the subjects. Data on side effects were also gathered by administering a 33-item questionnaire. The

subjects filled out the questionnaire according to how they felt just before going to sleep the previous night and for how they felt in the morning. After the six sessions were completed, each subject was interviewed about his experiences by a psychiatrist.

Results

The data were examined with regard to: sleep induction, sleep interruption and side effects.

Sleep Induction. Two measures of sleep induction were recorded: the time it took to get into bed after receiving the medication and the time to fall asleep after getting into bed. These two measures were totaled to produce a third measurement, total time to fall asleep after receiving the medication. Analyses of variance (repeated measurements) were carried out with each set of data and Duncan t-tests were used to test significance of difference among the various specific dosages and the placebo.

The analyses of variance of the *"time to bed"* measure showed no statistically significant difference among placebo and various dosages of $(-)\Delta^9$ THC. The *20* mg dose, however, tended to be the dose that induced the subjects to get into bed the soonest,

Analysis of variance for *"time to fall asleep"* after getting into bed just failed to reach statistical significance ($P < 0.10, > 0.05$); all three doses of $(-)\Delta^9$ THC tended to be more effective than the placebo in inducing sleep once the subjects were in bed.

The *"total time to fall asleep"* after receiving the medication was examined in a similar manner. The analysis of variance was significant at $P < 0.05$. The t-tests showed the 10 mg, 20 mg and 30 mg doses of $(-)\Delta^9$ THC each significantly shortened the "total time to fall asleep" after receiving THC as compared to the placebo. The 20 mg dose of $(-)\Delta^9$ THC shortened the time to fall asleep the most ; its mean difference from the placebo was 62 min ($P < 0.01$). The mean difference between placebo and 10 mg was *43* minutes ($P < 0.05$) and 54 mm between the

Table 1. Total time to fall asleep

Dosage	Time	Mean difference from placebo	*P* value from placebo
Placebo	180"	–	
10 mg THC	137	43	< 0.05
20 mg THC	118	62	< 0.01
30 mg THC	126	54	< 0.05

[a] Average time (minutes) after receiving THC.

Table 2. THC effects on sleep interruption

	THC			
	Placebo	10	20	30 mg
Total night (midnight—8 a.m.)				
Number of awakenings[a]	2.6	2.8	2.1	1.9
Time awake (minutes)[a]	50.0	50.0	51.7	51.7
Midnight—4 a.m.				
Number of awakenings	1.1	1.0	0.8	0.3
Time awake (minutes)	21.7	15.0	11.7	6.7
4 a.m.—8 a.m.				
Number of awakenings	1.5	1.8	1.3	1.6
Time awake (minutes)	28.3	35.0	40.0	45.0

[a] Average per subject.

placebo and 30 mg dose ($P < 0.05$). No statistically significant differences were obtained among the three dosage levels of (−)Δ^9 THC.

Sleep Interruption Data. To further explore the actions of (−)Δ^9 THC an examination was undertaken of sleep patterns during the night. Two measures of sleep interruption (i.e., after a subject had been observed as sound asleep) had been collected by the sleep observer who made a bed check every 15 min: the number of times a subject woke up, and the total time awake (if a subject was awake at the bed check, it was counted as 15 min awake).

When the data for the *total night* were analyzed, (−)Δ^9 THC, in comparison to the placebo, altered neither the number of times the subjects woke up nor the total time during the night (see Table 2).

To explore in more detail the duration of (−)Δ^9 THC activity the night was broken into two 4-hr periods (midnight to 4 a.m. and 4 a.m. to 8 a.m.) and the sleep interruption measures reanalyzed for the two periods of time separately.

Analyses of variance for the data in each 4-hr period revealed no statistically significant reduction in the number of awakenings, or in the minutes spent awake (see Table 2). In the first 4-hr period, however, there tended ($P = 0.10$) to be fewer awakenings and less time awake after (−)Δ^9 THC; the higher the dose given, the stronger the trend. In the later 4-hr period (4 a.m. to 8 a.m.), it was noted that increasingly *more* time was spent awake as the (−)Δ^9 THC dose increased, but none of the differences were statistically significant. These data suggest that the hypnotic action of the (−)Δ^9 THC was more pronounced between the hours of midnight and 4 a.m.

Side Effect Data. Side effects were recorded for both the Pre-Sleep period (during the time from drug ingestion to going to bed) and immediately Post-Sleep.

Only those side effects reported by more than one third of the subjects (i.e., four of them) in a given treatment condition are presented in the following tables.

Pre-Sleep, after the placebo, no side effects were reported by one third of the subjects. However, with increasing doses of (−)Δ^9THC,

Table 3. Pre-sleep side effects

Key phrases	Placebo	THC		
		10 mg	20 mg	30 mg
Feeling happy	0	4	2	3
Feeling silly	2	4	6	5
Thoughts, ideas hard to hold	2	5	5	2
Dry mouth	2	4	4	8
Hard to concentrate	1	5	5	7
Feel judgement ability is different	2	6	5	6
Body feels lighter, floating	0	0	4	2
Acting silly	0	1	4	4
Loss of time sense	0	3	4	7
Objects look different	2	3	6	6
Loss of control of thoughts	1	2	4	3
Thoughts moving faster	2	3	6	5
Fast thoughts interfere with sleep	1	2	4	5
Feel nauseous	0	0	0	4
Blurred vision	1	2	0	5
Funny taste in mouth	1	3	3	5
Loss of control of self	0	0	1	4
Things feel unreal, dreamlike	0	2	3	4
Objects hold attention longer	1	2	1	4
Time passes slower	0	1	2	5

Table 4. Post-sleep side effects

Key phrases	Placebo	THC		
		10 mg	20 mg	30 mg
Funny taste in mouth	0	2	5	1
Dry mouth	0	2	8	5
Dizziness or grogginess	3	3	6	5
Things feel unreal, dreamlike	0	2	2	4
Objects look different	0	1	2	6
Hard to concentrate	1	2	1	4
Thoughts moving faster	1	0	2	4
Thoughts, ideas hard to hold	1	2	2	4
Feel judgement ability is different	1	2	2	4

a greater number of side effects were reported by an increasing number of subjects. The side effects reported with the higher doses included subjective experiencing of perceptual disruptions or actual impairment of actions (not just of feelings of impairment-as with the lower dose), of greater loss of control and judgement, and of more physiologic involvement.

Past-Sleep (i.e., 9 hrs after ingestion of the medication), after the placebo and 10 mg dose of (−)Δ^9 THC, only one side effect (dizziness or grogginess) was reported by 3 of the 9 subjects. In addition to this feeling, after the 20 mg dose of (−)Δ^9 THC, a dry mouth (8 of 9 subjects) and a funny taste in the mouth (6 of 9 subjects) was experienced. A majority of the subjects still reported a variety of perceptual disruptions and speed of thought alterations the morning after having taken the highest dose (30 mg) of (−)Δ^9 THC.

In the interview conducted by the psychiatrist after each of the six sessions, the subjects described the effects of (−)Δ^9 THC as a "mild" or "mellow" high similar to an alcohol high. They reported the onset of action as occurring between 30-60 min after ingestion of the (−)Δ^9 THC. They further reported that the only side effect that bothered them was the racing of thoughts experienced after they got into bed. In the interview a number of subjects voiced being "spaced", "stoned", or "hung over" during the next day for a range of several to 24 hrs. As dosage increased, so did the degree and duration of this feeling, as well as the number of subjects reporting such experiences (after 10 mg, 1 subject; after 20 mg, 5 subjects; after 30 mg, 5 subjects). There seemed to be a pronounced subjective distinction between the 20 and 30 mg doses, with the higher dose producing a "stoned" effect for up to 24 hrs in one case and the 20 mg dose "slightly stoned" for up to several hours. Of possible heuristic value is that two subjects specifically mentioned decreased or no dreaming after 20 and 30 mg of (−)Δ^9 THC.

Discussion

The major aim of this study was to determine if any of the three dose levels of (−)Δ^9 THC used shortened the time it took mild insomniacs to get to sleep. In these individuals, whose average time to fall asleep after receiving the placebo was 3 hrs, each dose of (−)Δ^9 THC, significantly reduced the time it took to fall asleep after receiving the (−)Δ^9 THC. The most effective dose was the 20 mg level, which decreased this time by 62 mm, or approximately one-third of the placebo time, The time it took to get into bed was not effected by (−)Δ^9 THC, although the 20 mg dose tended to have a greater action than the other doses on this parameter. The hypnotic effects of all three doses of THC was more apparent on the time it took the subjects to go to sleep once in

bed ; the approximate average time to go to sleep after (—)Δ^9 THC being 40 min less than the placebo. It appears that the main effect of the (—)Δ^9 THC is on the subject once he gets into bed, rather than influencing him to get into bed sooner. It may be that the onset of drug action occurred about 1 hr after (—)Δ^9 THC administration and this happened to coincide with going to bed, or that the desire to get into bed heralded the perception of the onset of the action. The slight drop in sleep induction effectiveness when the dosage is increased from 20 to 30 mg might have been caused by increased temporal disruption noted after the higher dose (Le., the effect of being stoned or stimulated outweighed the desire to sleep, or made it harder to go to sleep).

Over the course of the whole night, (—)Δ^9 THC did not seem to effect sleeping pattern of the subjects once they were asleep. However, there tended to be a decrease in the number of sleep interruptions—along with an increase in the time slept-for the early part of the night only. These effects were also dose related. These data suggest that the hypnotic actions of (—)Δ^9 THC are relatively short lived. This effect is in contrast to the residual temporal or perceptual disorganization which was still reported in the Post-Sleep questioning.

The side effects reported after the higher doses were similar to those noted by Melges, Tinklenberg, Hollister and Gillespie [7,8] after marijuana and categorized by them as temporal disintegration. In the Pre-Sleep phase, the predominant general side effect at all doses of (—)Δ^9 THC seemed to be part of what they described as temporal disintegration. The number of subjects effected, and the intensity and degree of the temporal disorganization increased with dosage. At the higher dosages of 20 and 30 mg, one-third of the subjects also noted perceptual distortions and the feeling of loss of control of their thoughts and mind so strong that they felt it interfered with the sleep induction. The autonomic nervous system symptoms (dry mouth, funny taste, blurred vision, and nausea) were noted primarily at the 30 mg dosage.

A significant side effect, and the only one which the subjects complained of in the morning, aside from dry mouth, was a mild to moderate feeling of being “spaced”, “stoned”, or “hung over” as if from alcohol—particularly at the 30 mg doses. The length of time these effects lasted increased with the dosage, and in one case, lasted up to 24 hrs from a 30 mg dose, The people who received 20 mg, however, did not seem to mind the effect of being slightly stoned the next day, or felt any interference with their daily work function.

Although only two individuals noted decreased dreaming with higher doses of (—)Δ^9 THC, it may be worth mentioning the finding of Pivak, Zarcone, Dement, and Hollister [10], who found an increase in stage four sleep with ingestion of (—)Δ^9 THC.

Summary

(−)Δ^9 THC was found to significantly decrease the time it takes to fall asleep in physically healthy insomniacs. Once asleep, interruptions of sleep were not significantly altered over the whole night. The (−)Δ^9 THC tended to be associated with some decrease in awakenings in the first half of the night.

The primary side effect experienced at all three dose levels in the Pre-Sleep phase was a degree of temporal disorganization and mood alteration. There was an increase in intensity of side effects and number of subjects affected with increasing dosage. With the exception of experiencing dry mouth at the 10 and 20 mg dose, the 30 mg level of (−)Δ^9 THC was the only level in which the autonomic nervous system side effects were noted.

The most significant side effect, however, was a "hangover" phenomenon, or continued "high" the next day, with some residual of temporal disorganization. It increased in intensity and duration with increase in dosage. This "hangover" or "high" seems severe enough to eliminate the consideration of the 30 mg dose range of (−)Δ^9 THC for clinical use as an hypnotic.

Subsequent studies comparing (−)Δ^9 THC (at doses around 20 mg) with a standard hypnotic are in process.

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