PHARMACOLOGICAL REVIEWS
Vol. 23, No. 4

Printed in U.S.A.

ACTIONS OF VARIOUS MARIHUANA DERIVATIVES IN MAN

LEO E. HOLLISTER

Medical Investigator, Veterans Administration Hospital Palo Alto, California and Associate Professor of Medicine, Stanford University School of Medicine Stanford, California

Although tetrahydrocannabinol (THC) was identified as an active component of marihuana in the 1940's (1), two recent developments have given renewed impetus to clinical pharmacological studies of marihuana. First, identification of Δ^9-THC as the major THC isomer in natural cannabis materials (2) and second, the availability of techniques with gas-liquid chromatography (GLC) for measuring amounts of THC in natural materials. Both these developments permitted better quantification of dose than ever before possible.

Still, in all candor one must admit that dosage is still a problem in clinical pharmacological studies. First, even synthetic Δ^9-THC may vary somewhat depending upon its handling after its chemical synthesis. Any deterioration of this material between its time of synthesis and administration to man may result in actual doses less than putative doses. Use of such material as a standard for assay of THC content of native materials perpetuates the error. Second, the GLC assay of THC, because of the high temperatures used, decarboxylates the THC acids which are present to varying degrees in natural materials. As the THC acids may be pharmacologically inactive unless decarboxylated, any failure to do so may lead to a falsely high estimate of the dose of active material. Smoking such standardized natural materials reduces the error, as the heat of smoking probably decarboxylates most THC acids. However, when such materials are given orally, one has no assurance that the putative dose has been given, as the acids may or may not be decarboxylated by the body.

Not only are there problems in determining dose, but also in quantifying its delivery as well. When marihuana is smoked, a still uncertain and variable fraction of THC may be lost from smoke escaping into the air or exhaled incompletely absorbed from the respiratory dead space. Relatively little is lost by pyrolysis, as it is likely that the cannabinoids are volatilized in advance of the burning segment of the cigarette. The efficiency of the delivery of a dose by smoking has been estimated to range from 20 to 80%, but with experienced smokers with good technique, it should approximate 50% (13). Absorption of THC is rapid after smoking, so that effects may appear within seconds to minutes. If an active metabolite of THC is required for its effects, such as 11-hydroxy-THC, then conversion of THC must be extremely rapid, either in the lung itself or in the first circulation through the liver. Oral doses present other difficulties. Although one can be far more certain than in the case of smoking of the amount entering the body, its fate after that is far less certain. Some active material may be lost by decomposition or other metabolic change during absorption from the gastrointestinal tract or passage through the liver. In contrast to the immediate effects of the drug from smoking, those produced by oral ingestion are delayed by various time periods, presumably due to vagaries in absorption or different rates of

metabolism of the drug. As no method for the quantitative estimation of concentrations of THC or its metabolites in body fluids is available with usual chemical techniques, the actual concentrations of pharmacologically active materials obtained from the various routes of administration are still unknown.

Thus, at present, one must still regard dose-effect relationships as relative, rather than absolute. With this caveat in mind, it is possible to compare the effects of various marihuana isomers and homologues at various doses, both when these are administered orally or by smoking.

COMPARISON OF ORAL DOSES OF Δ^9-THC AND SYNHEXYL

When supplies of Δ^9-THC first became available to us, we decided that it might be appropriate to compare in our first study this material with the semisynthetic homologue, synhexyl. The latter compound represents a homologue of the Δ^{6a}-THC, differing only by having a hexyl rather than an amyl side-chain (fig. 1). Animal pharmacological studies had shown it to have marihuana-like activity (12). We thought such a comparison would be especially relevant, first because until fairly recently the assumption had been made that the Δ^{6a}-THC was the active isomer in plant materials, and second, because a good deal of prior experimentation had been done in man with the use of synhexyl. Should there have been a marked difference between synhexyl and Δ^9-THC, the entire body of literature regarding synhexyl would no longer be relevant. Luckily, some old supplies of synhexyl were still extant (furnished by Dr. Rodney Gwinn, Abbott Laboratories, North Chicago, Ill.) which had retained about 90% of the original chemical composition. We decided on the initial study to use the oral route, not only to take advantage of the greater certainty about the dose being given, but also because earlier studies of synhexyl had used this route. Administered orally, synhexyl had been found to have marihuana-like activity, and had been used clinically to treat withdrawal reactions to drugs and depressive reactions with mixed results (3, 15–17).

As previous studies with both Δ^9-THC (9) and with synhexyl had indicated a range of doses showing clinical activity, we chose to use initial doses of 30 mg of THC and 50 mg of synhexyl. Extensive experience with the use of other psychotomimetic drugs had led to the conviction that true double-blind studies of such agents against placebo are virtually impossible, so we elected simply to keep the dose and identity of drug secret, but not to impose a placebo control. Ultimately, we explored a range of oral doses from 10 to 70 mg of Δ^9-THC and 50 to 150 mg of synhexyl, both administered as a hydroalcoholic solution prepared from 95% ethanol solutions just before use (5).

Clinical syndromes were described from a combination of taped interviews, questionnaire data and self-rating mood scales obtained from the volunteer subjects. In general, the syndromes reported on taped interviews were rather similar between Δ^9-THC and synhexyl except for a slower onset of about 60 min and a somewhat more prolonged duration of action from equivalent doses of the latter drug. A composite clinical syndrome from oral doses of these drugs of the magnitude mentioned is shown in table 1. The same symptoms were confirmed by the

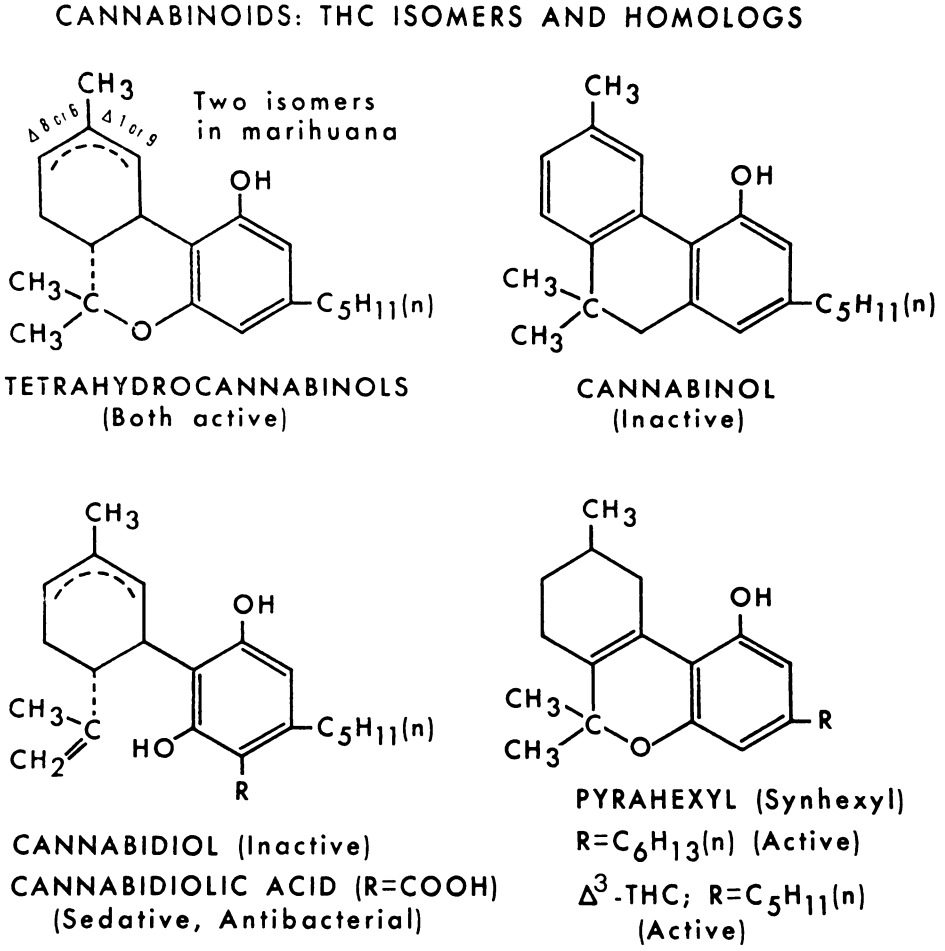

FIG. 1. Various cannabinoids and isomers and homologues of tetrahydrocannabinol of clinical interest.

questionnaire. Comparing questionnaire data from Δ^9-THC and synhexyl with previous data from experiments with lysergic acid diethylamide (LSD), we found that many symptoms were reported in common. Malaise was more often reported after LSD and drowsiness and sexual thoughts more often after marihuana; little wonder that marihuana is preferred for routine use by our youth. The pattern of changes reported on the mood scale was similar for both drugs, but more pronounced for Δ^9-THC due to the somewhat more potent doses used. Subjects felt friendlier early in the course, but less so toward the end, possibly because sedation interfered with sociability. Aggression also declined, probably again a reflection of sedation. Thinking was impaired throughout most of the period of drug action. Sleepiness tended to be a late phenomenon, probably because subjects were kept reasonably busy with experimental procedures during the early part

TABLE 1

Time-course of clinical syndromes, Δ^9-tetrahydrocannabinol (Δ^9-THC) and synhexyl

Time	Somatic	Perceptual	Psychic
30 min	Warm, cold, numb or tingling sensation; Sleepy, weak, heavy		
60 min	Same, plus: dry mouth; headache; circumoral numbness; palpitation	Colors; geometric patterns (eyes closed), blurred vision; hearing more acute	Anxiety; difficulty in thinking, speaking, concentrating Waxing and waning
90 min	Same, plus: thirst, hunger, tightness in chest; numbness in waves; jitteriness; increasing sleepiness	Same. plus objects slightly distorted	Same, plus: euphoria, elation, laughter; depersonalization; dreamlike states
2 hr	Same, plus: ataxia, poor coordination; breathing heavy	Same, plus: loss of time sense; buzzing or vibrating sensation	Same plus: loss of self-control; "drunk"
3 hr	Same, plus: fatigue; weightless, floating	Same, plus: visual patterns, images	Same, plus: dreams; thoughts racing; high point
4 hr	Same	Same	"Coming down"
5 hr	Same, plus: weak, fatigued, faint	Same, plus: time still slowed	Most effects beginning to wane
7 hr	Dizzy, sleepy, fatigued, headache; hangover	Hearing still acute; depth perception impaired	Dreams persist; still difficulty in thinking; less pleasant
24 hr	Some of above effects present in mild degree following largest doses, especially in synhexyl.		

of the course. Euphoria was confirmed and dizziness was marked. Based on various dose comparisons, we concluded that synhexyl was approximately one-third the potency of Δ^9-THC.

Both drugs produced similar physiological changes: slightly reduced systolic and diastolic blood pressure (with syncopal attacks in two subjects); increased pulse rate; no change in body temperature; muscle weakness demonstrated on the finger ergograph; reddened conjunctivae; mild tremor; unchanged deep tendon reflexes; unchanged pupils; and normal electrocardiograms. A number of laboratory measurements were made, selected largely on the basis of their having been changed in other experiments by drugs such as LSD (4). Levels of plasma-free fatty acids, often an indicator of an exciting action of a drug, were unchanged; elevations are often seen after excitant drugs, such as LSD. Plasma glucose values were unchanged, despite previous reports of lowered levels. Total leukocytes and eosinophils were not significantly changed, although the former tended to increase and the latter decrease. Creatinine and phosphorus clearance rates were temporarily decreased, the only biochemical change similar to that from LSD. The blood cell and urinary clearance changes are probably best explained as non-specific reactions to the stress of the experiment.

It seemed clear that the clinical effects of synhexyl were quite similar to those of Δ^9-THC in most respects. The relatively slow onset and longer duration of action suggested to us that synhexyl might have to be metabolized to an active metabolite before becoming active. As subsequent work suggests that the same biotransformation may be important with Δ^9-THC, the process may only be slower in the case of synhexyl.

COMPARISON OF Δ^9-THC, SYNHEXYL AND Δ^{6a}-THC ADMINISTERED BY SMOKING

For many years, Δ^{6a}-THC was considered to be the naturally-occurring THC accounting for most pharmacological activity of marihuana. Some recent work suggested that it was not active, a turn of events that would have been both surprising and intriguing (9). It seemed that it might be of some interest to determine whether or not this double-bond isomer of THC was active, especially in comparison to its homologue, synhexyl. When it became possible to obtain a very small amount of Δ^{6a}-THC (through the courtesy of Prof. R. Mechoulam, School of Pharmacy, Hebrew University of Jerusalem) we decided to compare it with the other THC isomer and homologue. For this study, we elected to use smoking as the route of administration, mainly to conserve the extremely small amount of material available.

As the physics of cigarette smoking is much more complicated than one might ordinarily believe, we decided to use a commercially made cigarette as the vehicle for administering our doses of marihuana constituents. This meant limiting our volunteer subjects to those already tolerant to nicotine and taking the risk of some unexpected interaction between marihuana and nicotine. We have subsequently used a commercially available placebo cigarette made from lettuce as the vehicle for drug, but the smoke is so unpleasant that the decision to use nicotine-containing cigarettes was not regretted. Quantities of materials were put into ethanol solutions which were then laid into the cigarettes, with a thin, long needle; the excess ethanol was evaporated under a stream of nitrogen and the cigarettes stored in sealed tubes under nitrogen and refrigeration until ready for use.

Sets of four cigarettes were made to contain: (a) Δ^9-THC, 12 mg, obtained from extraction of natural marihuana; (b) synhexyl, 15 mg; (c) Δ^{6a}-THC, 15 mg; and (d) a placebo containing marihuana extract from which all cannabinoids had been extracted previously. The individual tubes containing these cigarettes were identified only by number, with the order of assignment of smokes being random. Trials were conducted at least 48 hr apart. Particular attention was paid to deep inhalation of smoke, retention in the lungs for several seconds, and smoking to a butt length of 5 mm or less by use of a short, unfiltered holder (7).

The impossibility of a true double-blind experiment was again made clear. Although the mere technique of smoking a nicotine-containing cigarette in the same manner as one might smoke a marihuana cigarette produced unusual symptoms, these were distinctly different from those produced by the active cigarettes. Only one subject of six reported more symptoms from the placebo cigarette than from an active cigarette; in this case symptoms were somewhat greater than with the synhexyl-containing cigarette. The usual symptoms from

intense smoking of the regular cigarettes were transient feelings of dizziness and lightheadedness.

The type of symptoms and their time course are shown in table 2, which represents the type of reaction most often observed after smoking of the cigarettes containing Δ^9-THC. Although symptoms of similar type were frequently observed after the other two cigarettes, their intensity and duration were somewhat less. Our estimate of comparative potencies was that Δ^9-THC was from 3 to 6 times as potent as the other two materials, which appeared to be of about equal potency.

Thus, it appeared that Δ^{6a}-THC was indeed active and that the assumption of the past was vindicated. The presence of the slightly longer side-chain in synhexyl did not afford any major change in activity or potency. It also was clear that one possible explanation for placebo effects from marihuana smoking where the content of THC is absent or minimal may be due to the technique of smoking in the particular fashion required. Obviously, other explanations for placebo effects from marihuana also obtain.

COMPARISONS BETWEEN Δ^9-THC AND OTHER PSYCHOACTIVE DRUGS

The Lexington group compared effects of smoked Δ^9-THC (doses of 75 to 225 μg/kg) with those of LSD given intramuscularly (doses of 0.5 to 1.5 μg/kg). Subjective effects between the two drugs were not readily distinguished, but objective differences were marked: LSD increased body temperature, increased both systolic and diastolic blood pressures, increased deep tendon reflexes and dilated pupils, while THC had none of these effects (10). Our own retrospective comparison of the effects of orally administered Δ^9-THC and LSD came to similar conclusions regarding objective differences. We thought that in terms of subjective effects, Δ^9-THC produced less total impairment of function with more euphoria and dreamlike states than LSD at comparable doses and that, unlike the latter drug, sedation was a prominent feature with THC, most subjects falling asleep (6).

We compared doses of marihuana extract calibrated to 0.5 mg/kg of Δ^9-THC content with doses of 950 mg/kg of ethanol and 0.2 mg/kg of dextroamphetamine, all taken orally. A marihuana placebo control was also used, against which

TABLE 2

Syndromes from 12 mg of Δ^9-tetrahydrocannabinol (Δ^9-THC) smoked
3–4 min —numbness, tingling in extremities; light-headedness; "floating"; loss of concentration
10–15 min—palpitation; sweating; weakness; tremulous; tachycardia; reddened eyes
20–30 min—euphoria; mental impairments; loss of time sense; dry mouth
30–60 min—increasing sleepiness
60–90 min—clearing
Syndromes from 15 mg Δ^{6a}-THC smoked
Similar but milder than Δ^9-THC
Syndromes from 15 mg synhexyl smoked
Similar but milder than Δ^9-THC more dry mouth and burning in throat
Syndromes from marihuana placebo
Dizziness; light-headed; tingling in hands—usually no more than 10–20 min in duration

changes from the other drugs were measured (8). On the basis of self-reports on a mood scale, dextroamphetamine made subjects less drowsy, more stimulated and more active, while ethanol and marihuana were alike in decreasing activity, especially later in the course. The same distinctions obtained in regard to two psychometric tests, based on freehand drawings or arithmetic problems, where dextroamphetamine enhanced performance (even in non-fatigued subjects) while ethanol and marihuana tended to impair it. On a combined time estimation-time production test, productions of time were shortened by all drugs, but in this case, marihuana stood apart from the other drugs in approximating most closely the time interval to be produced, presumably due to the characteristic subjective slowing of time that it and other hallucinogens produce. Psychomotor performance on simple reaction time was impaired both by ethanol and marihuana. None of the drugs affected cognitive performance measured by the digit-symbol substitution test or perception of the vertical as measured by the rod-and-frame test. Despite the fact that marihuana is considered to have a biphasic clinical action with initial stimulation and euphoria followed later by sedation, clinically there was little resemblance to the stimulant properties of dextroamphetamine. It does, however, have ethanol-like sedative properties.

Another comparison of ethanol and marihuana used two doses of the latter, one smoked and one taken orally. The smoked dose was equivalent to 9 mg of Δ^9-THC, the oral dose was equivalent to 90 mg, both being compared to doses of 950 mg/kg oral doses of ethanol (11). The subjects, who were all heavy users of marihuana, showed little effect from the rather large acute dose of ethanol, and were scarcely able to distinguish active smoked marihuana from placebo. They uniformly distinguished the active oral dose, which was considerably stronger than the active smoke as measured by symptom reports. Both forms of marihuana increased pulse rate and time estimation; they had no effect on time production, the rod-and-frame test, and digit-symbol substitution. Because of the remarkable tolerance of these subjects to ethanol, as well as to a monumental dose of marihuana (if the putative oral dose was correct), the possibility of some cross-tolerance between alcohol and marihuana was raised.

Marihuana cigarettes calibrated to deliver 2.5 or 5 mg of Δ^9-THC (based on an assumption of 50% efficiency in delivery of dose) were smoked either alone or in combination with oral intake of 15 g of ethanol per 50 pounds of body weight (14). The higher dose of THC produced impairment in performance on both mental and motor tasks, although there was relatively little difference between the two doses of marihuana in terms of impairment. Addition of alcohol increased impairment still more as compared with marihuana alone, an effect which was appreciated subjectively as well. Once again, the similarity between marihuana and alcohol in impairing performance and in the additive interaction between the two drugs was apparent. One might expect similar additive effects between marihuana and other sedatives, particularly those of the barbiturate type.

FUTURE STUDIES OF Δ^9-THC AND HOMOLOGUES

For the past 2 years, human studies with pure Δ^9-THC have been prohibited pending the usual toxicological studies required by the Food and Drug Adminis-

tration of any new drug to be used for human experimentation. While such a policy seems consistent with established clinical pharmacological practice, it is one thing to insist upon such precautions in the case of a chemical never before given to man and quite another to insist upon them in the case of a chemical currently being self-administered by upwards of 200 million persons in the world. Curiously, experimenters have been perfectly free in the intervening period to administer to man equivalent doses of Δ^9-THC in the form of marihuana extracts, even though the latter contain many other components of unknown nature, quantity and activity. As one might have expected from prior studies which attempted to find an LD50 for marihuana extracts of unknown THC content, the doses of Δ^9-THC required for establishing acute toxicity were extremely large. As quantities of this material were in short supply, due to difficulties in synthesis, work was slow and only recently has approval again been given for resuming work started 3 years ago. Thus, it is not remarkable that so little is currently known about various THC isomers and homologues.

Should the same elaborate precautions be required for the study of isolated marihuana constituents in the future, progress will continue to be slow. It would be nice to determine once and for all whether or not cannabinol and cannabidiol are active in man, or whether when given with Δ^9-THC they may interact to enhance activity. As other natural marihuana constituents are identified and either isolated or synthesized, one would like to determine as early as possible their clinical relevance. The question of whether an active metabolite of Δ^9-THC, 11-hydroxy-Δ^9-THC, is active in man as it is in animals is still unresolved. Apparently, it can be formed from THC given to man and it has been proved to have pharmacological activity in animals. If these important questions are to be deferred for years while yields of materials are increased from milligrams and grams to kilograms, so that extensive acute and chronic toxicity studies can be done, then these questions are likely to remain unanswered for some time.

REFERENCES

1. Adams, R.: Marihuana. Bull. N. Y. Acad. Med. 18: 705–730, 1942.
2. Gaoni, Y. and Mechoulam, R.: Isolation, structure, and partial synthesis of an active constituent of hashish. J. Amer. Chem. Soc. 86: 1646–1647, 1964.
3. Himmelsbach, C. K.: Treatment of the morphine abstinence syndrome with a synthetic cannabis-like compound. S. Med. J. 37: 26–29, 1944.
4. Hollister, L. E.: Chemical Psychoses. LSD and Related Drugs. Charles C Thomas, Springfield, Ill., 1968.
5. Hollister, L. E., Richards, R. K. and Gillespie, H. K.: Comparison of tetrahydrocannabinol and synhexl in man. Clin. Pharmacol. Ther. 9: 783–791, 1968.
6. Hollister, L. E. and Gillespie, H. K.: *In* Drugs and Youth, ed. by J. R. Wittenborn, H. Brill, J. P. Smith and S. A. Wittenborn. Charles C Thomas, Springfield, Ill., 1969.
7. Hollister, L. E.: Tetrahydrocannabinol isomers and homologues: contrasted effects of smoking. Nature (London) 227: 968–969, 1970.
8. Hollister, L. E. and Gillespie, H. K.: Marihuana, ethanol and dextroamphetamine. Mood and mental function alterations. Arch. Gen. Psychiat. 23: 199, 1970.
9. Isbell, H., Gorodetsky, G. W., Jasinski, D., Claussen, U., Spulak, F. V. and Korte, F.: Effects of (—)Δ^9-transtetrahydrocannabinol in man. Psychopharmacologia 11: 184–188, 1967.
10. Isbell, H. and Jasinski, D.: A comparison of LSD-25 with (—)-Δ^9-transtetrahydrocannabinol (THC) and attempted cross tolerance between LSD and THC. Psychopharmacologia 14: 115–123, 1969.
11. Jones, R. T. and Stone, G. C.: Psychological studies of marijuana and alcohol in man. Psychopharmacologia 18: 108–117, 1970.
12. Loewe, S.: Studies on the pharmacology and acute toxicity of compounds with marihuana activity. J. Pharmacol. Exp. Ther. 88: 154–166, 1946.

13. MANNO, J. E., KIPLINGER, G. F., BENNETT, I. F., HAINE, S. AND FORNEY, R. P.: Comparative effects of smoking marihuana or placebo on human motor and mental performance. Clin. Pharmacol. Ther. 11: 808–815, 1970.
14. MANNO, J. E., KIPLINGER, G. F., SCHOLZ, N., FORNEY, R. B. AND HAINE, S. E.: The influence of alcohol and marihuana on motor and mental performance. Clin. Pharmacol. Ther. 12: 202–211, 1971.
15. PARKER, C. S. AND WRIGLEY, F.: Synthetic cannabis preparations in psychiatry (I) synhexyl. J. Ment. Sci. 96: 276–279, 1950.
16. STOCKINGS, G. T.: Brit. Med. J. 1: 271, 1948.
17. THOMPSON, L. J. AND PROCTOR, R. C.: The use of pyrahexyl in the treatment of alcoholic and drug withdrawal conditions. N. C. Med. J. 14: 520–523, 1953.