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# DOSE-RESPONSE RELATIONSHIPS TO CANNABIS IN HUMAN SUBJECTS

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Relatively few clinical studies have been reported in which the relationship between the dose of cannabis and effect has been systematically explored. The reasons for this are centered around the chemical nature of the drug and its varied mode of use. Before the mid-1960's, there was general confusion as to the identity of the pharmacologically active principal of the crude material. Since that time there is general agreement that at least the principal active constituent of cannabis is (−)$\Delta^9$-*trans*-tetrahydrocannabinol or more commonly $\Delta^9$-THC. This is, of course, the pyran nomenclature rather than the monoterpenoid system. Several sensitive methods of assay for cannabinols have been developed, most of these gas-liquid chromtographic procedures. In addition, synthetic $\Delta^9$-THC has become more available so that studies with better dosage control have been possible. Thus, most of this discussion will be derived from reports of the last 4 or 5 years.

There is a body of literature which supports the concept that there is a pharmacological difference between oral ingestion and the inhalation of smoke from cannabis products. These reported differences have clouded the issue of the overall effects of the drug, but are probably most clearly understood now in terms of administered dose of active ingredients and their relative rates of absorption. Walton (8) reviewed most of the pertinent literature up through 1938 and points out the differences between the use of cannabis resin (hashish) and smoked cannabis. When writing of the experiences of hashish users, the emphasis is placed on the hallucinatory episodes and the long duration of action. On the other hand, when smoked in the form of marihuana the reports center on the euphoria, and the more subtle alterations of time and space perception. Implicit in Walton's review is the concept of dose-effect.

In 1944, the results of studies sponsored by the Mayor's Committee on Marihuana were published (5). A portion of this report deals with clinical studies on cannabis. Doses used were usually 2 and 5 ml of a cannabis extract or three to five marihuana cigarettes. An attempt was made to relate observed effects to the administered dose and in general it was found that larger doses produced more profound effects. This was particularly true on such parameters as static equilibrium, hand steadiness, and complex reaction time where small doses produced definite effects and large doses larger effects. On other test parameters such as simple reaction time and speed of tapping the smaller doses used produced only slight or negligible effects while the larger doses produced definite

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impairment. Pulse rate was found to be increased with all doses by either route of administration. These effects cannot, however, be defined in terms of $\Delta^9$-THC content of the materials used.

One of the earliest systematic studies on dose-effect relationships with drugs of this class was not done with the natural products of cannabis, but with one of the Adams' compounds. This work was done during the late 1950's and early 1960's and has been recently reported in a variety of sources, the most complete of which is the Army report released in 1970 (7). Sim studied the response of a number of volunteer subjects to orally administered graded doses of the compound known as EA1476 or DMHP or the 3-(1,'2'-dimethylheptyl) analogue of $\Delta^{6a,10a}$THC. The doses used ranged from 10 to 60 $\mu$g/kg. Pulse rates in his subjects increased and his data show a rough correlation of dose and effect but with some apparent plateauing at the higher doses (40 to 60 $\mu$g/kg). Orthostatic hypotension was a prominent finding, but again was not dose-dependent and in fact seemed more pronounced at intermediate levels. Data on the effects on psychomotor tests indicated most clearly the anticipated increasing response with increasing dose. Over a range of 10 to 60 $\mu$g/kg of EA1476, there was a definitive increased impairment on the Texas Battery (number facility and flexibility of closure), the Purdue pegboard (manual dexterity) and the Stromberg Manual Dexterity Test. In all instances, the impairment in performance correlated with the anecdotal reports of behavior and mood of the subjects.

Isbell *et al.* (2) reported on studies of dose-response analysis of $\Delta^9$-THC in man with pulse rate and subjective questionnaire data as assay parameters. In their studies, $\Delta^9$-THC was administered both by smoking and by mouth. When smoked, the drug was loaded on the middle one-third of a tobacco cigarette in alcoholic solution and then dried. For oral administration, the alcoholic solutions were dispersed in cherry syrup. Appropriate placebos and double-blind techniques were used. Doses were 50 and 200 $\mu$g/kg by inhalation or 120 and 480 $\mu$g/kg orally. Their data indicate highly significant, positive dose-effect relationship on both pulse rate and subjective responses. They were also able to compare the potency of THC by the two routes and found remarkable agreement between the two assay parameters. With pulse rate, they found the drug to be 2.6 times as potent when smoked and with subjective response data the potency ratio was 3.0, smoking *versus* ingestion.

The doses reported in their smoking experiments were the quantities applied to the cigarettes. Subsequent reports indicate that only 50% of the THC content is actually delivered in the smoke (1, 5). It is, therefore, likely that the doses received in the smoke by the subjects in the study of Isbell *et al.* (2) were actually 25 and 100 $\mu$g/kg. The only significance of this observation is that the THC may be actually five to six times as potent by inhalation when delivered dose rather than cigarette content is considered. It would also be of interest to know how much THC remained in the butts of the cigarettes used in these studies.

Weil *et al.* (9) conducted a study in which the effects of two doses of cannabis were compared to placebo on several parameters. The portion of their study

most relevant to this discussion concerns itself with their naive subjects, nine in number, who received all doses administered. Their chronic users were exposed only to the high dose which is reported as 2 g of cannabis containing 0.9 % of $\Delta^9$-THC. Their low dose was 0.5 g of the same material. The placebo marihuana consisted of the outer covering of the stalks of male hemp plants. Tobacco, placebo and mint leaves were used as fillers in all cigarettes except that the high dose contained no placebo material.

All cigarettes were marked to a uniform length with an ink line and subjects were instructed to smoke to this line. Thus, although the cigarettes contained 4.5 and 18 mg of THC (low *versus* high dose), there is no way of knowing the amount of residual THC in the butt which remained.

More pertinent perhaps is the fact that the data on pulse rate do not indicate a dose-response relationship. Both high and low dose gave increases of about 16 beats per min compared to 8 for placebo. In addition, their data indicate that with the high dose the pulse rate had returned to normal by 90 min whereas with the low dose it had not.

Weil *et al.* (9) presented data that indicated that their eight chronic users given a single 2.0 g dose of cannabis had an increase in pulse rate of 33 beats per min, double that of their naive group. However, the chronic users were not studied with the same control criteria of placebo and double-blind conditions. One possible explanation may be that the naive subjects, in spite of instructions and observation, inhaled less of the putative dose than did the chronic smokers. This, however, would not explain the fact that the chronic users were less affected on psychomotor performance than the naive.

Dose-response trends were reported by Weil *et al.* (9) for both the digit symbol substitution test and for the pursuit rotor in their naive subjects.

Melges *et al.* (6) studied the effects of multiple doses of THC administered orally as a standardized cannabis extract on mental functioning. Their doses were calibrated for $\Delta^9$-THC content and contained 0, 20, 40 or 60 mg. These were administered to eight volunteers in a double-blind randomized block design. Their test procedures were designed to evaluate recent memory function and temporal organization. Four test situations were reported: digit span, forward and backward (a straight memory task); serial subtraction by seven's which is less dependent on recent memory and more dependent on sustained attention and long-term memory; and a goal-directed serial alternation (GDSA) task which depends on retention of recent input, mental coordination and serially indexing recent memories relevant to a goal.

They found that GDSA was profoundly affected with a dose-dependent impairment in performance. This has been termed "temporal disintegration." Dose-dependent impairment in digit span was also demonstrated. On the other hand, the serial subtraction by seven's was not significantly affected, although their data indicate a tendency toward impairment with increasing dose. It is apparent from their data that impairment of recent memory is a dose-dependent phenomenon.

We have also been concerned with various aspects of dose-dependent altera-

tions in performance and in physiological parameters (3, 4). These studies were done in collaboration with Dr. Joseph Manno, currently at Auburn University and Dr. Robert B. Forney. Subjects were male volunteers between the ages of 21 and 30 years. A brief medical history revealed no evidence of disease or of gross psychiatric abnormality. All subjects were chosen from either cigarette smokers or marihuana smokers, but none were daily users of marihuana. Also rejected were those with a history of use of potent hallucinogens.

All marihuana was administered by smoking. The marihuana was of Asian origin and assayed at 3.8% $\Delta^9$-THC content with only a trace of $\Delta^8$-THC. A placebo was prepared by exhaustively extracting marihuana until no cannabinoids were detected by gas-liquid chromatography analysis. This placebo marihuana was also used to dilute the 3.8% material for preparation of cigarettes containing graded doses. Experiments were done which demonstrated that only 50% of the THC content of the cigarette was actually available in the smoke. Cigarettes were, therefore, prepared on the basis of "delivered dose." That is, a cigarette that contained 10 mg of THC was considered a 5-mg dose. Doses used in our experiments were 2.5 and 5.0 mg in one study and 6.25, 12.5, 25 and 50 $\mu$g/kg in another. In each experiment, a randomized block design was used with double-blind procedures; each subject received each treatment at 1-week intervals.

All subjects were familiar with the smoking process and were asked to inhale deeply, hold the smoke, and to consume the cigarette within a period of 10 min. All cigarettes weighed 0.5 g and the placebo was indistinguishable from authentic marihuana by taste, smell or burning characteristics. All were consumed down to the charred paper by use of forceps to hold the butt. Analysis of the residue indicated that less than 10% of the THC remained.

In one study, the purpose was to examine both the effects of alcohol-marihuana combinations and varying doses of marihuana as measured by THC content. The parameters measured were pulse rate, subjective effects (Cornell Medical Index), motor performance on a pursuit meter and verbal performance with delayed auditory feedback. We were able to demonstrate an additive effect with alcohol in these studies. However, our dose-response relationships were not as clear-cut on some parameters as had been anticipated. Significant dose-response curves were developed for pulse rate and for subjective sensations. Figure 1 shows the pulse rates for 12 subjects under our different test conditions. The lower curve is the dose-response curve to THC at doses of 0, 2.5 and 5 mg delivered in the smoke. The upper curve represents the same doses of THC in the same subjects, but with a blood concentration of 0.05% ethanol. Our lowest dose of THC, 2.5 mg, produced a mean increase in pulse rate of 15 beats per min above placebo level.

In contrast, our dose-response curves for motor and mental function as measured by the pursuit meter and the delayed auditory feedback (DAF) indicated very little difference between the high and low dose. This is shown in figure 2 which is a summary of the data from four different pursuit meter tests. The lower curve is the response to 0, 2.5 and 5 mg of THC while the upper curve

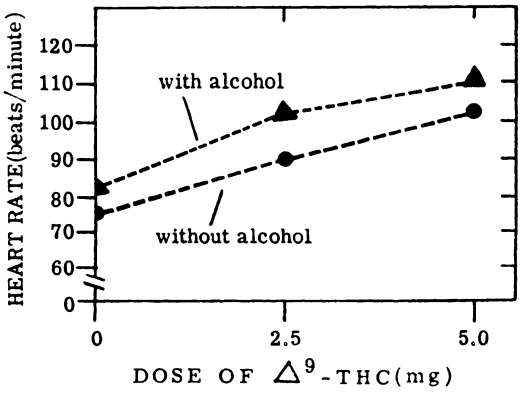


FIG. 1. Mean heart rate of 12 subjects administered doses of (—)$\Delta^9$*trans*-tetrahydrocannabinol ($\Delta^9$-THC) calibrated marihuana cigarettes. Lower curve, marihuana alone; upper curve, same doses in the presence of ethanol at a concentration of 0.05% in blood. (From Joseph E. Manno, Glenn F., Kiplinger, Norman Scholz and Robert B. Forney: The influence of alcohol and marihuana on motor and mental performance. Clin. Pharmacol. Ther. **12**: 202-211, 1971.)

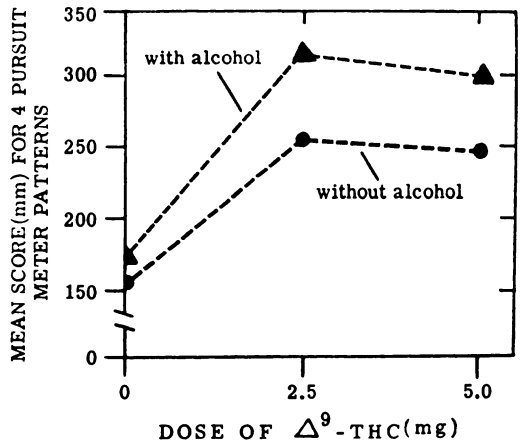


FIG. 2. Mean score for 12 subjects on four pursuit meter patterns after doses of (—)$\Delta^9$-*trans*-tetrahydrocannabinol ($\Delta^9$-THC) administered as calibrated marihuana cigarettes. Lower curve, marihuana alone; upper curve, same doses in the presence of ethanol at a concentration of 0.05% in blood. (See reference 4.)

is the same only in the presence of alcohol, 0.05%. Our feeling at this time was that perhaps there was some plateauing effect, or that our instruments would not allow the distinction between the two doses we were using. In order to examine this phenomenon, we decided to extend the dose response analysis to lower doses and to administer THC on a μg/kg basis. Doses chosen were 6.25, 12.5, 25 and 50 μg/kg with a placebo control. Parameters measured were essentially the same except that we added a measure of static equilibrium, and the

Addiction Research Center Inventory for marihuana effects. These results are summarized in figures 3, 4 and 5.

Figure 3 shows both the magnitude and the duration of the effect on pulse rate. If the rate at 20 min post-smoking is used as the dependent variable against dose, there is a highly significant linear dose-response curve. Notice that the duration is also dose-dependent in that larger doses have not yet returned to baseline at the termination of the experiment.

As an aside from the dose-response data, Dr. Thomas Bright working in our laboratories has shown that the increase in pulse rate can be blocked by the *beta*-adrenergic blocker, propranolol. The blocker was administered in four divided doses totaling 160 mg during the 24 hr before challenge with a cigarette calibrated to deliver 25 $\mu$/kg of THC. Appropriate control with intravenous isoproterenol demonstrated that *beta*-blockade had been established.

Figure 4 shows the data for the pursuit meter on four different patterns. Again, there is a significant increase in error score which is linearly dependent on dose.

Figure 5 shows the effect of the same dose on static equilibrium. This is measured with an electronic device which records sway as electrical counts. Increasing counts indicate increasing sway. Stability is also measured under conditions designed to remove visual and proprioceptive cues. Thus, there are four sets of

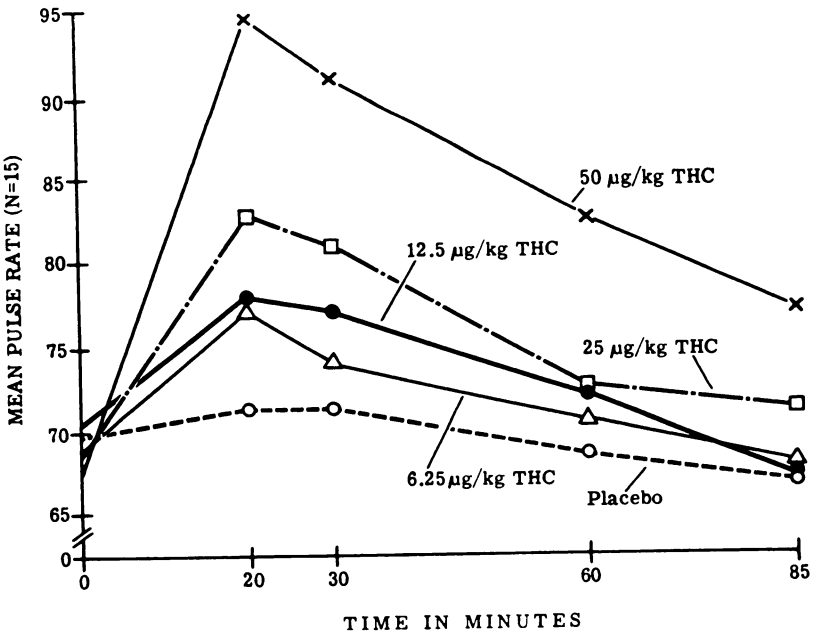


FIG. 3. Magnitude and duration of the effect of doses of (—)$\Delta^9$*trans*-tetrahydrocannabinol ($\Delta^9$-THC) on pulse rate. All doses administered to the same 15 subjects as calibrated marihuana cigarettes. (From Glenn F. Kiplinger, Joseph E. Manno, Bruce E. Rodda, and Robert B. Forney: Dose-response analysis of the effects of tetrahydrocannabinol in man. Clin. Pharmacol. Ther. **12**: 650–657, 1971.)

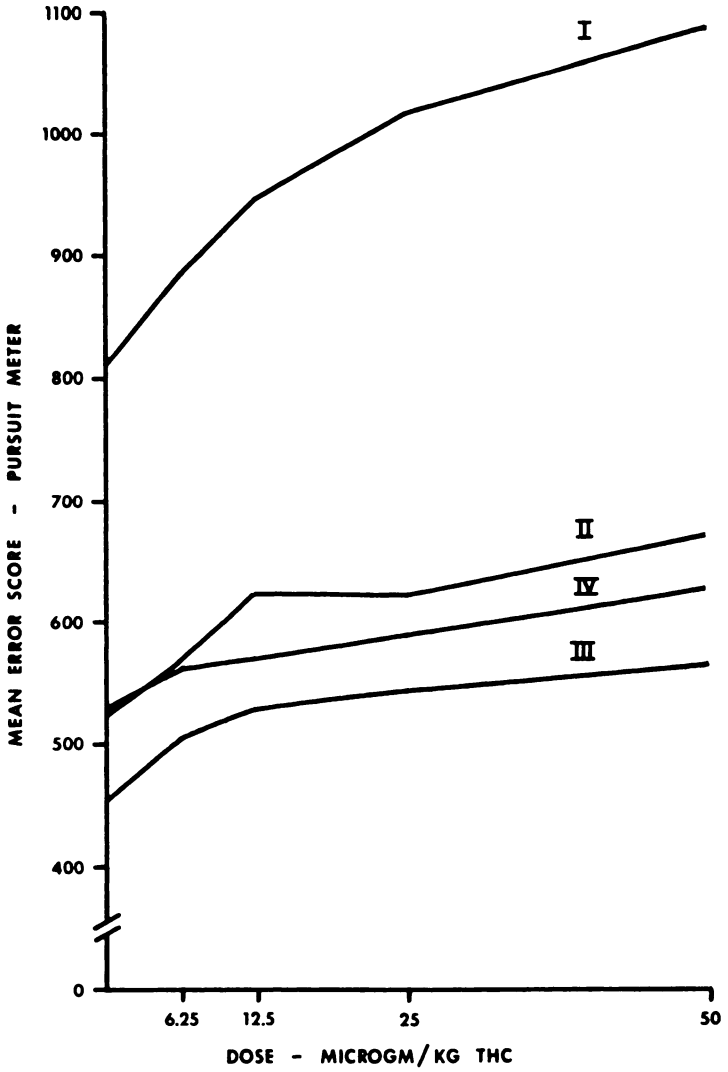


FIG. 4. Mean error score for 15 subjects on four different pursuit meter patterns. Doses of (—)$\Delta^9$-*trans*-tetrahydrocannabinol ($\Delta^9$-THC) were administered as calibrated marihuana cigarettes. Ordinate, error score is millimeter of deviation from a standard trace; abscissa, dose of $\Delta^9$-THC; roman numeral refers to the four patterns used in the study. All curves show a significant dose-dependent increase. (See reference 3.)

curves: normal conditions (eye open and fixed for far vision); eyes closed; eyes open, but with a vibrator on the stand to remove or confuse proprioceptive input from the feet and legs; and eyes closed with vibrator on. All curves were parallel indicating no particular sensitivity of one condition over another.

In summary, as one might predict for an active pharmacological substance, there is a relationship between administered dose of cannabis, its constituents or

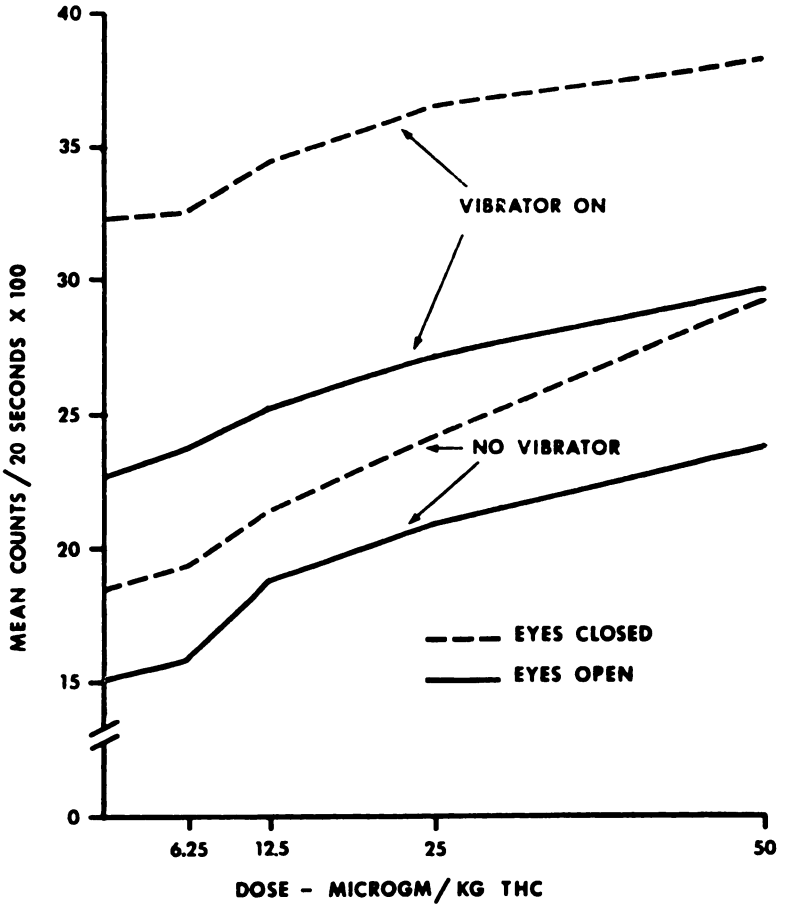


FIG. 5. Effects of (—)$\Delta^9$-*trans*-tetrahydrocannabinol ($\Delta^9$-THC) on static equilibrium in 15 subjects. Doses were administered as calibrated marihuana cigarettes. Ordinate, electrical counts as a measure of sway in the standing position; abscissa, dose of $\Delta^9$-THC. See text and reference 3 for explanation of the four conditions. All curves show a significant dose-dependent increase in sway.

analogues, and the response observed. Perhaps the most consistent of these is the tachycardia characteristically produced by THC. This has been demonstrated by Isbell *et al.* (2) by both oral and inhalation routes and by us with the use of inhalation. Curiously, Weil *et al.* (9) found no such relationship in their naive subjects even though chronic users did show a pronounced tachycardia with a single dose of the same material.

Other parameters for which dose-response relationships have been demonstrated include: several psychomotor measurements (3, 4, 7); positive responses on subjective questionnaires (2, 3, 4); mental performance and short-term memory (3, 4, 6).

The hallucinatory experiences and transient psychoses produced by these

derivatives are also part of the dose-response phenomenon in that they are generally observed with doses far in excess of those required for euphorigenic effects.

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