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# Vehicle and Route of Administration as Parameters Affecting Operant Behavioral Effects of Δ⁹-Tetrahydrocannabinol

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**Abstract** □ Four vehicles for Δ⁹-tetrahydrocannabinol were compared after intraperitoneal and subcutaneous administrations, using the disruption of food-reinforced, operant behavior of rats as the test system for cannabinoid activity. Aqueous suspensions based on polyvinylpyrrolidone, polysorbate 80, and a polysorbate 65–sorbitan monolaurate combination all were effective vehicles for intraperitoneal or subcutaneous absorption of the cannabinoid. An olive oil solution was poorly effective. The polyvinylpyrrolidone dispersion appeared to have the most rapid onset of action, while the polysorbate 65–sorbitan monolaurate combination had the longest duration of action.

**Keyphrases** □ Marijuana—effect of vehicle and route of administration of Δ⁹-tetrahydrocannabinol on operant behavior, rats □ Δ⁹-Tetrahydrocannabinol—effect of vehicle and route of administration on operant behavior, rats □ Cannabinoid activity—studied by operant behavioral effects in rats, different vehicles and routes of administration

The major psychoactive constituent in marijuana (*Cannabis sativa*) is generally accepted to be (−)-Δ⁹-*trans*-tetrahydrocannabinol (I). The elucidation of the structure and synthesis of I has prompted extensive investigation of its pharmacological and behavioral effects in both animals and man (1, 2). However, the extreme aqueous insolubility of I has made parenteral administration difficult. A number of different aqueous suspensions and oil solutions have been tried by various researchers, but no single preparation has found widespread acceptance. At times, conflicting results between studies have been attributed to differences in the drug vehicle or mode of administration.

The present study compared four such vehicles administered *via* two routes of injection to evaluate the drug effect in a test system previously shown to be sensitive to Δ⁹-tetrahydrocannabinol (3–5). The measure chosen was the depression of operant responding of rats for food reinforcement. In this experiment, both the onset and duration of action of I were examined as a function of eight combinations of vehicle and route of injection.

## EXPERIMENTAL

Twenty-four male Wistar rats (225–300 g.) were trained to bar-press for food reward on a fixed-ratio-50 (FR50) schedule of reinforcement; the 50th lever-press resulted in the delivery of a 45-mg. Noyes food pellet. The animals were given 60-min. experimental sessions on 5 days each week, with supplementary postsession feeding sufficient to maintain them at 80% of their free-feeding weights. The operant chambers were controlled by solid-state programming equipment. Cumulative recorders and digital counters were used for data collection. Before initial drug sessions, each rat received 4–5 weeks of training until performance stabilized so that there was less than 10% variation in responses per session over three consecutive sessions.

The four preparations of Δ⁹-tetrahydrocannabinol compared in this experiment were: Vehicle A, olive oil solution; Vehicle B, a 1% polysorbate 80[1] dispersion in saline; Vehicle C, a suspension with 1% polysorbate 65[2] and 1% sorbitan monolaurate[3] in 0.9% saline, as described by Moreton and Davis (6); and Vehicle D, a 10% polyvinylpyrrolidone suspension in 0.9% NaCl, prepared according to the procedure of Fenimore and Loy (7). Each vehicle was tested both intraperitoneally and subcutaneously. The dose of I used was 10 mg./kg. given at an injection volume of 1.0 ml./kg. body weight. The injections of I were given at weekly intervals on Wednesday, vehicle alone was given on Tuesday and Thursday, and saline was injected on Monday and Friday. To examine the relative duration of action of I as well as the time of onset, injections were given either immediately prior to the operant session or 1, 2, or 3 hr. before. At least six determinations were made for each vehicle–route–time combination. The drug effect was assessed by comparing the bar-press performance on drug days to performance on the preceding vehicle control session.

## RESULTS AND DISCUSSION

Operant responding following the intraperitoneal or subcutaneous injection of the four vehicles alone did not differ from that following saline administration or no injection. In Table I the effects of Δ⁹-tetrahydrocannabinol upon responding are summarized as a function of the route–vehicle–time combinations. The total number of responses during the 1-hr. test session is expressed as a percentage of the responses per hour in the prior vehicle control session. Gen-

[1] Tween 80.
[2] Tween 65.
[3] Arlacel 20.

Table I—Effects of $\Delta^9$-Tetrahydrocannabinol on Fixed-Ratio-50 Performance in Rats: Vehicle and Route of Administration as Parameters Affecting Onset and Duration of Behavioral Disruption

| Route of Injection | Drug Vehicle | Percent of Predrug Control Responses per Hour[a] 1st hr. Postinjection | 2nd hr. Postinjection | 3rd hr. Postinjection | 4th hr. Postinjection |
|---|---|---|---|---|---|
| Intraperitoneal | A, olive oil | 102 | 48 | 54 | 105 |
| | B, polysorbate 80 | <1 | <1 | <1 | 72 |
| | C, polysorbate 65 plus sorbitan monolaurate | 4 | <1 | 8 | 43 |
| | D, polyvinylpyrrolidone | <1 | <1 | 9 | 90 |
| Subcutaneous | A, olive oil | 100 | 88 | 83 | 101 |
| | B, polysorbate 80 | 54 | 32 | 44 | 59 |
| | C, polysorbate 65 plus sorbitan monolaurate | 65 | 64 | 68 | 55 |
| | D, polyvinylpyrrolidone | 15 | <1 | 20 | 83 |

[a] Each value is the mean of six observations. $\Delta^9$-Tetrahydrocannabinol dose = 10 mg./kg.

erally, all three aqueous suspensions of I showed a prompt onset of action within 1–5 min. following intraperitoneal administration, whereas a significant effect of I in the oil solution did not occur within the 1st hr. after injection. During the 2nd and 3rd hr. after administration of I in aqueous suspension, suppression of operant responding continued, whereas I in oil reduced response output only one-half. When I was administered subcutaneously in these vehicles, a slower onset was observed, as expected. Compound I in Vehicle D appeared to take effect by the subcutaneous route more rapidly than in either Vehicle B or C. Again the olive oil solution was poorly absorbed. Peak behavioral suppression occurred during the 2nd hr. following subcutaneous injection in Vehicles B and D.

Concerning the duration of behavioral depression, data for the 4th hr. after intraperitoneal administration indicate that I in Vehicle C gave the longest activity. In either Vehicle B or C, I given *via* the subcutaneous route still produced significant operant depression 4 hr. postinjection; in Vehicle D, it was only minimally effective. With I in oil, no effect was observed in the 4th hr. after either intraperitoneal or subcutaneous administration.

In a comparison of vehicles for $\Delta^9$-tetrahydrocannabinol, Sophia *et al.* (8) measured the effects of I in four vehicles on the latency to convulsion in mice after electroconvulsive shock. Only the intraperitoneal route was studied. They found that a polyvinylpyrrolidone suspension in saline and a 10% propylene glycol–1% polysorbate 80 suspension in saline were most effective. Polysorbate 80–saline and bovine serum albumin in saline were found to be poorly absorbed preparations. In another recent study (9), emulsions of polysorbate 80 or polyvinylpyrrolidone plus sesame oil in saline were also found to be suitable vehicles for parenteral administration.

By utilizing operant behavioral techniques, the present experiment indicated that $\Delta^9$-tetrahydrocannabinol is absorbed effectively from aqueous suspensions but poorly absorbed from oil solutions following intraperitoneal administration. Absorption from a subcutaneous site is somewhat delayed but is significant. Vehicle D gave the most rapid absorption of the four preparations studied by both routes of administration. To obtain a prolonged duration of action, Vehicle C appeared to be most effective.

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