Marihuana: importance of the route of administration

Conventionally marihuana is used, or rather abused, by inhalation. In this respect it more closely resembles tobacco than alcohol with which it has most often been compared from a behavioural point of view. Yet, surprisingly enough, most experiments on the pharmacological, neurochemical, or behavioural effects of marihuana have relied on an intraperitoneal administration of extracts of cannabis or pure 1-Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive constituent.

In working with synthetic Δ^9-THC (Idänpään-Heikkilä, Fritchie & others, 1969) we were impressed by its great water insolubility which led us to question just how well it might be absorbed *via* the various conventional routes of administration. Tritiated-Δ^9-THC with a specific activity of 250 μCi/mg was synthesized (Idänpään-Heikkilä, Fritchie & others, 1969) and administered to rats in Tween-80 as a suspension intraperitoneally and intravenously. Animals were killed at various times and autoradiographs prepared using the technique previously described (Ullberg, 1968; Idänpään-Heikkilä, Vapaatolo & Neuvonen, 1968). ^{3}H-Δ^9-THC administered intraperitoneally remains in the abdominal cavity, with little absorption and distribution to other tissue, including the CNS (Fig. 1A and B). The same dose given intravenously was distributed throughout the body, including the CNS, within 5 min (Fig. 1C). Preliminary experiments also indicated good absorption and distribution after inhalation (Ho, Fritchie & others, 1970). A discrepancy exists between the known effective dose in man (100–250 μg/kg range inhaled) (Isbell, Gorodetzsky & Jasinski, 1967; Weil, Zinberg & Nelsen, 1968), and that used in most animal studies—10–25 mg/kg, and even as high as 00 mg/kg (intraperitoneally).

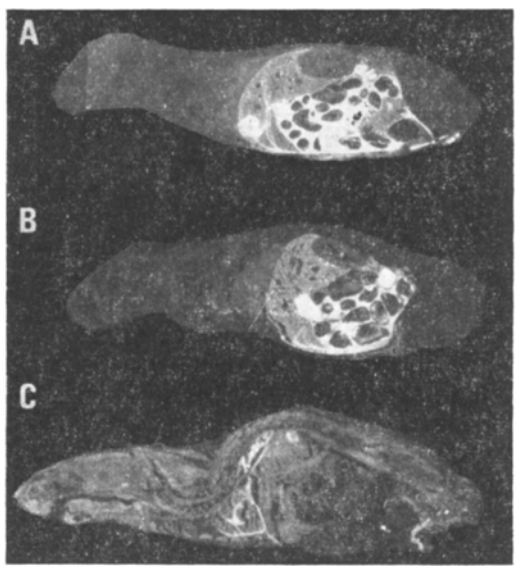

FIG. 1. Distribution of radioactivity (light areas) in mice 15 min (A) and 2 h (B) after intraperitoneal injection and 5 min (C) after intravenous injection of ^{3}H-Δ^9-THC.

Although measurable pharmacological and behavioural effects do occur after intraperitoneal administration of relatively large doses, this obviously is not the best route for the study of the compound.

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Injectible dispersion of Δ^9-tetrahydrocannabinol in saline using polyvinylpyrrolidone

The intravenous administration of Δ^9-tetrahydrocannabinol (Δ^9-THC), an active principle of marihuana, is complicated by the extreme insolubility of the compound in aqueous media. We wish to report a preparation which appears to be well tolerated physiologically and is stable physically and chemically over extended periods of time.

This medium consists of a dispersion of Δ^9-THC in normal saline using polyvinylpyrrolidone PVP) as a carrier.

A suspension in the amount of 100 ml containing 1 mg Δ^9-THC/ml is prepared as follows: 40 ml of an ethanol solution containing 100 mg Δ^9-THC (a standard preparation of synthetic Δ^9-THC as distributed by the National Institute of Mental Health) is mixed with 30 ml of a 10% ethanol solution of PVP (polyvinylpyrrolidone K-30, average mol wt 40 000, Matheson, Coleman and Bell). The ethanol is removed by heating to 60° under a stream of dry nitrogen, or, alternatively, by vacuum rotary evaporator. Normal saline (sodium chloride injection, U.S.P., Abbot Laboratories) is then added with thorough mixing to bring the volume to 100 ml.

The resulting milky white dispersion when stored under refrigeration and in the absence of light shows no deterioration or isomerization of the Δ^9-THC, as determined by gas chromatographic analysis, over at least two months.

The PVP concentration should be at least 20 times that of the Δ^9-THC to produce a homogeneous suspension, thus there is some limitation to the amount of Δ^9-THC that can be effectively suspended without raising the viscosity of the medium to impractical levels. Preparations containing 2·5 mg/ml have been administered intravenously to rats without difficulty, and use of these dispersions in infusion pump administration to catheterized animals has been successful.

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