5 Δ^9-THC Hemisuccinate in Suppository Form as an Alternative to Oral and Smoked THC

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Abstract

Although Δ^9-tetrahydrocannabinol (THC) has demonstrated utility for several medicinal applications, several studies have reported the inconsistent bioavailability of the oral soft gelatin capsule formulation, because of erratic absorption and variable first-pass metabolism of THC. This problem limits the utility of THC for its approved indications, and also prevents efficient assessment of other potential therapeutic applications. In an effort to overcome these pharmacokinetic limitations, we have explored the utility of various ester prodrugs of THC in suppository formulations as alternatives for effecting the systemic delivery of THC. Studies designed to characterize the bioavailability and efficacy of these preparations are reviewed here. In addition, studies designed to confirm the behavior of THC-hemisuccinate (THC-HS) as a prodrug were conducted. In rodents and dogs, intravenous administration of THC and THC-HS produced identical pharmacological responses (hypothermia and potentiation of thiamylal sleep times in mice; bradycardia in dogs) except at very high doses. Pharmacokinetic evaluations after intravenous and rectal administration of THC-HS also showed that the parent ester could not be detected in plasma, but that THC and its metabolite were detected in a fashion consistent with the immediate hydrolysis of THC-HS to THC in the absorption process or in the plasma. Administration of the THC-HS via suppositories resulted in excellent bioavailability, sustained plasma levels of THC, and improved efficacy as compared to the oral formulations, suggesting the feasibility of this route for the delivery of THC in various therapeutic applications.

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1. INTRODUCTION

Δ^9-tetrahydrocannabinol (THC) is the primary psychoactive constituent in marihuana (*Cannabis sativa* L.), and is likely responsible for marihuana's other interesting pharmacological actions. THC has been approved by the Food and Drug Administration (FDA) for the control of nausea and vomiting associated with chemotherapy and, more recently, for appetite stimulation in AIDS patients suffering from the wasting syndrome. Cannabinoids, however, also possess pharmacologic attributes that have led to proposed use for symptomatic treatment in several other disorders, such as glaucoma *(1),* migraine headache *(2,3),* and other pain syndromes *(4),* spasticity *(4),* anxiety *(5,6),* and depression *(4,7).* It is because of these promising therapeutic applications that public debate has arisen over the legalization of marihuana for medicinal purposes. Balancing the therapeutic use of a drug against its abuse potential is often a delicate issue. This is particularly true in regard to marihuana smoking, for which the purported medicinal uses are used to justify legalization and of marihuana. Thus, there are legal, political, and social, as well as medical issues to be addressed.

One point well argued by the medicinal marihuana proponents is the fact that the legally available THC, prepared as a soft gelatin capsule formulation and sold as Marinol®, is very expensive and lacks consistency in its effects. The latter point could be explained by the fact that oral THC has erratic absorption from the gastrointestinal tract, and is subject to a marked first-pass effect in the liver, resulting in extensive metabolism *(8,9).* This results in the formation of high levels of 11-OH-THC, which may have undesirable side effects. Pharmacokinetic studies indicate bioavailability is only 10–20% in healthy adults *(9),* and this may be further decreased by emetic episodes in patients. A recent meta-analysis revealed a poor or partial response in approximately 65% of 750 courses of oral therapy *(10).*

In an effort to overcome problems with the consistent delivery of THC, we have devoted a considerable effort to identifying a formulation and route of administration with improved bioavailability. An evaluation of several different esters as prodrugs of THC demonstrated that the hemisuccinate ester (THC-HS) afforded substantial bioavailability from a suppository base *(11),* whereas THC itself totally lacks bioavailability from suppositories *(12).*

The formulation of THC as the hemisuccinate ester in suppositories appears to overcome all the problems associated with the oral preparation and shows consistent bioavailability in animal studies *(11,13).* Preliminary clinical investigations show promise for this formulation *(14–16).*

The purpose of this report is to review the bioavailability studies carried out on the hemisuccinate ester (THC-HS) and to establish whether THC-HS is truly acting as a prodrug of THC. We therefore compared the pharmacological and toxicological effects of intravenous THC-HS and THC, in dogs and rodents, in addition to the evaluation of the blood levels of THC, and its major metabolite (THC-COOH) after iv administration in monkeys.

METHODS

2.1. Comparison of the Toxicity and Pharmacology of THC and THC-HS in Mice

ICR Swiss mice weighing 25–30 g were housed in group boxes of five each, and two boxes were allocated to each study group. On the day of the experiment, each mouse was temporarily restrained in a plastic cylinder to allow access to a tail vein for iv injections. Immediately after injection, the mice were returned to their home cages. The groups received the vehicle (ethanol:Alkamuls [Rhone-Poulenc, Research Triangle Park, NC] saline, 1:1:8),