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BRIEF COMMUNICATION

Bypassing the First-Pass Effect for the Therapeutic Use of Cannabinoids

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MATTES, R. D., L. M. SHAW, J. EDLING-OWENS, K. ENGELMAN AND M. A. ELSOHLY. *Bypassing the first-pass effect for the therapeutic use of cannabinoids.* PHARMACOL BIOCHEM BEHAV **44**(3) 745–747, 1993.—An oral formulation of Δ-9-tetrahydrocannabinol (THC) in sesame oil (Marinol®) is at present used for the management of chemotherapy-related nausea and emesis. However, due partly to poor bioavailability, its efficacy is variable. To circumvent possible metabolism in the gut and a first-pass effect by the liver, a suppository formulation of THC hemisuccinate ester was prepared. Administration of the suppository containing 11.8 mg of the hemisuccinate ester (equivalent to 9 mg THC) to three adult females (two of whom had previously exhibited low plasma drug levels following a 10-mg dose of the oral formulation) led to a marked and sustained elevation of plasma drug levels. Areas under the curves for plasma THC were more than 30-fold higher than after oral dosing. The suppository was well tolerated. The higher and more sustained plasma drug level achieved with this new formulation should enhance its antiemetic efficacy.

Marijuana Cannabinoid Antiemetic Suppository Drug

CANNABINOIDS have demonstrated efficacy in the management of chemotherapy-related nausea and emesis, but a recent metaanalysis revealed a poor or partial response in approximately 65% of 750 courses of oral therapy (3). This may be because the bioavailability of the oral formulation of this lipophilic drug is low due to degradation in the gut and a large first-pass effect by the liver (1,5). We monitored plasma levels of Δ-9-tetrahydrocannabinol (THC) and its primary carboxylic acid metabolite (11-nor-Δ-9-THC-COOH) in 57 healthy adults by the method of electron-capture negative chemical-ionization mass spectrometry (4) following double-blind, placebo-controlled acute dosing (15 mg males, 10 mg females) with Marinol® capsules (the only FDA-approved form of this drug). The mean (± SD) areas under the curves (AUC) for the subsequent 6-h period for THC and the metabolite were 3.13 ± 4.78 and 39.59 ± 69.65 ng/ml × h, respectively. These low levels and high variability reflect the large proportion of individuals without measurable plasma drug concentration (84, 61, and 57% of participants 2, 4, and 6 h postdosing for THC; 70, 30, and 15% of participants 2, 4, and 6 h postdosing for the metabolite). Pharmacokinetic studies indicate bioavailability is only 10–20% in healthy adults (5) and this could be decreased in a vomiting patient.

Reliable elevations of plasma drug levels can be achieved by inhalation (smoking) or IV delivery of THC (1), but these methods are either not feasible or acceptable to most ambulatory, nonhospitalized patients. Recently, it was reported that administration of Δ-9-THC hemisuccinate ester via rectal suppository to dogs resulted in a bioavailability of 67% (2). The present article provides the first human data on plasma drug levels and selected physiological and behavioral effects following administration of this suppository.

METHOD

Following FDA approval to administer this formulation to three adults, a single 11.8-mg dose (equivalent to 9 mg THC) was given to three marijuana-experienced healthy females.

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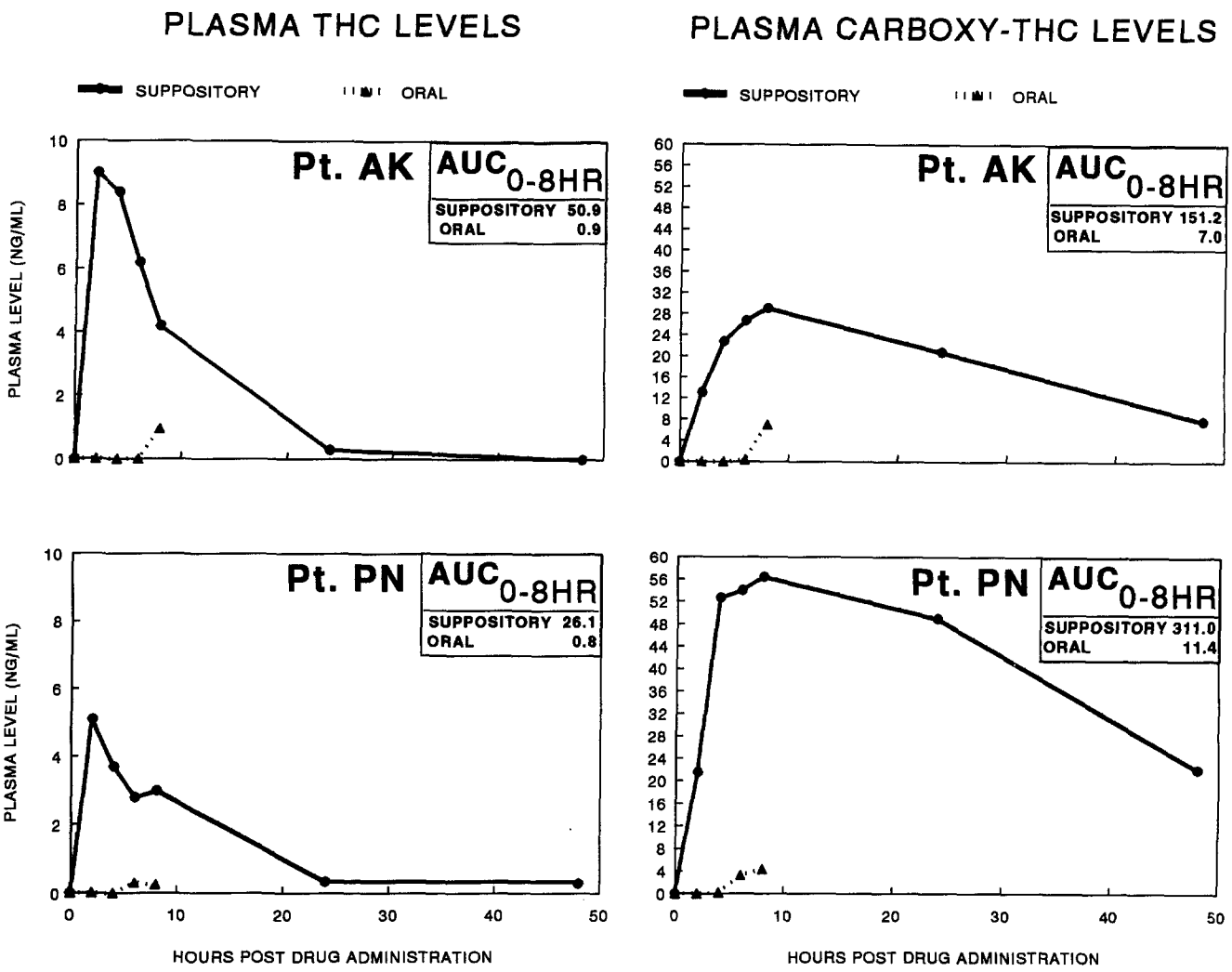

FIG. 1. Plasma Δ-9-tetrahydrocannibinol (THC) and carboxy-THC levels of two individuals following drug administration via oral capsule and rectal suppository. Offsets present area under the 0- to 8-h curve data following both routes of drug delivery.

Participants had fasted overnight and consumed a small standard breakfast immediately prior to drug delivery at 0900 h. Based upon analysis of a urine sample provided upon arrival, each participant had a negative THC screen (EMIT DAU test for cannabinoids, 20-ng/ml threshold concentration). Plasma samples were collected 2, 4, 6, 8 (all subjects), 24, and 48 (two subjects) h postdosing. Blood pressure, heart rate, and self-rated "high" were recorded prior to dosing and 2, 4, and 6 h later. Readings were taken by a technician naive with regard to participant drug status. This study was approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania.

RESULTS

Two participants had taken 10 mg THC (Marinol®) orally approximately 1 month earlier and exhibited low plasma THC and metabolite levels over an 8-h period. The enhanced drug availability following suppository use is demonstrated in Fig. 1. The offsets depict 8-h THC and carboxylic acid metabolite AUC values. Values for the third subject were 72.8 ng/ml × h (THC) and 95.8 ng/ml × h (metabolite). In the two individuals providing data on plasma drug levels after oral and rectal administration, the 8-h AUC for the suppository was 33- and 56-fold higher for THC and 27- and 22-fold higher for the carboxylic acid metabolite.

Data on blood pressure, heart rate, and self-rated high are presented in Table 1. The suppository was well tolerated with no marked changes of blood pressure or heart rate noted. Psychoactive effects were low to moderate; individual peak values were 2, 6, and 6 on a 10-point intensity scale.

DISCUSSION

This suppository formulation led to a marked and sustained elevation of plasma drug levels in all three participants. It is particularly noteworthy given that two participants had displayed low plasma drug levels after oral administration of a comparable dose. This route of drug delivery may enhance

TABLE 1

BLOOD PRESSURE, HEART RATE, AND SELF-RATED "HIGH" VALUES OF THREE FEMALES BEFORE AND 2, 4, AND 6 h AFTER A SINGLE 11.8-mg DOSE OF THC HEMISUCCINATE ESTER ADMINISTERED BY RECTAL SUPPOSITORY

	Hours Postdosing			
Subject	0	2	4	6
Systolic pressure (mm Hg)				
AK	100	110	110	100
JW	120	120	100	100
PN	120	120	120	120
Diastolic pressure (mm Hg)				
AK	60	60	60	60
JW	60	60	55	55
PN	60	75	60	80
Heart rate (beats/min)				
AK	72	86	80	72
JW	92	84	100	104
PN	65	64	72	68
High (1 = not at all, 10 = extremely)				
AK	1	5	6	4
JW	1	2	2	2
PN	2	4	6	6

antiemetic efficacy relative to oral ingestion in a more acceptable format to patients than IV administration or smoking marijuana.

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