J. Pharm. Pharmacol. 1988, 40: 374–375
Communicated September 25, 1987

Prolonged apparent half-life of Δ^1-tetrahydrocannabinol in plasma of chronic marijuana users

EVA JOHANSSON, STIG AGURELL*†, LEO E. HOLLISTER‡, MAGNUS M. HALLDIN*† *Department of Pharmacognosy, Uppsala University, BMC, S-751 23 Uppsala, *Department of Pharmacology, Karolinska Institute, S-104 01 Stockholm, and †Astra Alab AB, S-751 85 Södertälje, Sweden; ‡Veterans Administration Medical Center, Palo Alto, CA 94304, USA*

Abstract—The aim of this study was to characterize the elimination half-life of Δ^1-tetrahydrocannabinol in blood plasma in chronic marijuana users. The subjects smoked four cigarettes during a two day period, each cigarette containing 15 mg deuterium-labelled Δ^1-tetrahydrocannabinol. The plasma concentrations of deuterium-labelled tetrahydrocannabinol were measured for 13 days using gas chromatography-mass spectrometry equipped with selected ion monitoring. The elimination half-life for Δ^1-tetrahydrocannabinol in blood plasma was calculated to be $4{\cdot}1 \pm 1{\cdot}1$ days (range 2·9–5·0 days) from the two week plasma level curves. Albeit the present results are based upon a small sample, an elimination half-life of Δ^1-tetrahydrocannabinol in blood plasma of about 4 days is more in line with apparent half-life excretion of Δ^1-tetrahydrocannabinol metabolites in the urine of chronic marijuana smokers.

The frequent abuse of cannabinoid preparations has, during the last fifteen years, focused attention on the pharmacokinetic properties of Δ^1-tetrahydrocannabinol (Δ^1-THC), the psychoactive component in cannabis preparations, in man. Several studies have attempted to determine the elimination half-life of Δ^1-THC in plasma after smoking marijuana (Ohlsson et al 1982; Barnett et al 1982; Wall et al 1983; Lemberger 1973; Hunt & Jones 1980). Values ranging between 2–57 h have been suggested by different investigators. Differences between chronic and naive users have been reported. In these earlier studies the plasma levels were only measured up to 72 h after administration mainly due to low sensitivity of the assay. One can assume that the terminal elimination phase was not reached at this point, and that the half-life should be much longer, as indicated in recent animal studies (Garrett & Hunt 1977; Harvey et al 1985; Leuschner et al 1986).

This study was conducted to address this question and obtain a more exact value of the elimination half-life of Δ^1-THC in chronic marijuana users. Plasma concentrations in three subjects were measured by selective ion monitoring for an extended time period after smoking $[^2H_2]\Delta^1$-THC.

Materials and methods

Labelled compounds. A deuterium-labelled analogue of Δ^1-THC, 1″—$[^2H_2]\Delta^1$-THC, was administered to the subjects and $[^2H_7]\Delta^1$-THC (1″-^{2}H-2″-^{2}H-3″-^{2}H-4″-^{2}H-5″-$^2H_3$-Δ^1-THC) was used as internal standard. The compounds were synthesized as described earlier (Ohlsson et al 1976).

All solvents used were of analytical grade and redistilled twice.

Subjects. Three men who used cannabis chronically (daily smoking of more than one marijuana cigarette) volunteered to take part in the study. Recent use was verified in part by a positive EMIT test for cannabinoids in the urine on at least three occasions before the experiment.

The study was approved by the Institutional review board at Stanford University (USA) and Karolinska Institute (Sweden). The subjects received verbal and written information about the study, and written consent was obtained. The volunteers were free to withdraw from the study at any time, and asked to abstain from all cannabis use as well as other illicit drugs during the experimental period.

Treatment and experimental design. The subjects smoked two marijuana cigarettes (obtained from National Institute on Drug Abuse, Bethesda), spiked with 15 mg $[^2H_2]\Delta^1$-THC each, on two consecutive days giving a total dose of 60 mg. The two cigarettes were smoked in the morning with a 4 h interval between them. The total dose smoked was estimated to be about 14 mg/cigarette after analysis of the cigarette butts (Agurell & Leander 1971). The loss of $[^2H_2]\Delta^1$-THC by pyrolysis, side stream smoke and expired air was not determined.

Heparinized blood samples (5–10 mL) were withdrawn three days before smoking $[^2H_2]\Delta^1$-THC (blank sample), during the days of administration and during the discontinuation phase of 28 days. The plasma was immediately separated and kept frozen (−20°C) until the time of analysis.

Sample analysis. 50 μL of internal standard (5·22 ng $[^2H_7]\Delta^1$-THC) was added to the plasma with volumes of about 3 mL. The plasma samples were extracted with organic solvent, purified by liquid chromatography and silylated with BSTFA (*N,O-bis*-(trimethylsilyl)trifluoracetamide; Pierce Chemical Co.) according to a method described earlier (Ohlsson et al 1976, 1979).

Selected ion monitoring. Mass fragmentographic measurements were made with a LKB 2091 GC-MS instrument. The trap current and the ionizing potential were 50 μA and 50 eV, respectively. The retention time of the compounds were about 3·5 min at 230°C. The intensities of the molecular ions of unlabelled Δ^1-THC (m/z 386), the administered compound (m/z 388) and the internal standard (m/z 393) were recorded continuously. Separations were made on a fused silica capillary GC-column (Durabond-liq.phase DB 17-30W, 25 μm). The present assay is capable of measuring Δ^1-THC in plasma to 20 pg mL^{-1}.

Pharmacokinetic analysis. The terminal elimination half-life was calculated using the curve fitting program 'Elsfit' available from University of California, San Francisco (Peck et al 1984).

Results and discussion

Plasma levels of $[^2H_2]\Delta^1$-THC, were analysed in three male chronic marijuana users for 28 days after termination of drug use. However, the plasma levels after day 15 were below the detection limit of 20 pg mL^{-1}. The plasma concentration vs time profile of the subjects (RH, DA and PE) are shown in Fig. 1.

The elimination half-lives were determined to 2·9, 5·0 and 4·5 days for the three subjects RH, DA and PE, respectively, with a mean value of $4{\cdot}1 \pm 1{\cdot}1$ days. These values are considerably higher than those reported earlier (about 24 h) after smoking in both heavy and naive users (Ohlsson et al 1982; Barnett et al 1982). Values of 25 h and 29–36 h were reported by Wall et al

‡ Present address: Harris County Psychiatric Center, Houston, TX 77225-0249, USA.
Correspondence to: M. M. Halldin, Dept of Drug Metabolism, Astra Alab AB, S-151 85 Södertälje, Sweden.

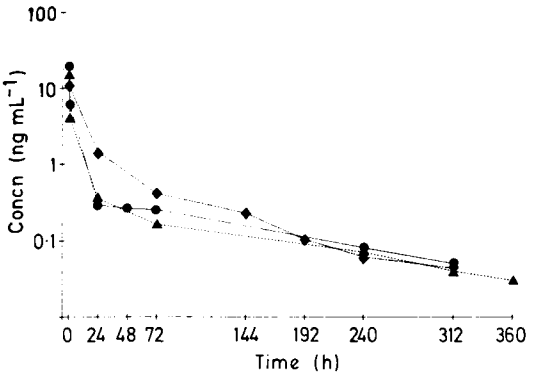

FIG. 1. Plasma concentration-time profiles of $[^2H_2]\Delta^1$-THC after smoking in three male chronic marijuana users.

(1983) in males and females after oral and i.v. administration, respectively. However, the plasma levels were only followed up to 72 h in these studies which was not enough to determine fully the terminal elimination phase. Lemberger (1973) has reported the half-life to be 28 h and 56 h in naive and heavy users, respectively, after i.v. injection of $[^{14}C]\Delta^1$-THC. These values were approximations since they were based on estimated radioactive unchanged Δ^1-THC extracted from the plasma during a 3 day period.

Our present findings are more in agreement with those reported using animal models. Harvey et al (1985) and Leuschner et al (1986) were able, using GC-MS with metastable ion monitoring (detection limit about 5 pg mL^{-1}), to follow the plasma levels after a single i.v. administration in rabbits (1 mg kg^{-1}) and mice (30 mg kg^{-1}). The calculated elimination half-life was between 33–66 h in rabbits, and about 20 h in mice. Somewhat longer half-lives (up to 8 days) were reported in dogs after administration of radiolabelled Δ^1-THC (Garrett & Hunt 1977).

Our results are in general agreement with the long excretion pattern, up to 77 days with an apparent half-life of 1–10 days, of Δ^1-THC metabolites seen in the urine of chronic marijuana users (Dackis et al 1982; Cridland et al 1983; Ellis et al 1985). An elimination half-life in the plasma of 3–5 days indicates that THC is accumulated in a deep compartment, most likely in the fat tissues as proposed by several investigators based on animal experiments (Agurell et al 1970; Bronson et al 1984), and slowly released back to the blood and further metabolized before excretion. Enterohepatic circulation of Δ^1-THC could also contribute to this long half-life, but probably only to a minor degree.

Even though the plasma levels are not high enough to give any psychoactive effects, they can probably contribute to some of the side effects reported after long term use (Nahas 1984).

No isotope effect was expected from the compound smoked, since the positions of the incorporated deuterium atoms are only affected by metabolism to a very small degree in man (Widman et al 1985). No major abstinence symptoms were observed in any of the subjects during the discontinuation period.

Our study shows that previous studies using a sampling period of 72 h were too short to detect the long elimination phase of Δ^1-THC.

We thank Maria Wetterdahl and Hamp Gillespie for skilful technical assistance, and Jan-Erik Lindgren for helpful advice when recording the mass spectra. This study was supported in part by grants DA-03926-02 and DA-00424-9, awarded by the National Institute on Drug Abuse.

References

Agurell, S., Leander, K. (1971) Stability, transfer and absorption of cannabinoid constituents of cannabis (hashish) during smoking. Acta Pharm. Suec. 8: 391–402

Agurell, S., Nilsson, I. M., Ohlsson, A., Sandberg, F. (1970) On the metabolism of tritium-labelled Δ^1-tetrahydrocannabinol in the rabbit. Biochem. Pharmacol. 19: 1333–1339

Barnett, G., Chiang, C. W. N., Perez-Reyes, M., Owens, S. M. (1982) Kinetic study of smoking marijuana. J. Pharmacokinet. Biopharm. 10: 495–506

Bronson, M., Latom, C., Nahas, G. G. (1984) Distribution and disposition of delta-9-tetrahydrocannabinol (THC) in different tissues of the rat. In: Agurell, S., Dewey, W. L., Willette, R. E. (eds) The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects. Academic Press, Orlando, pp 309–317

Cridland, J. S., Rottanburg, D., Robins, A. H. (1983) Apparent half-life of excretion of cannabinoids in man. Human Toxicol. 2: 641–644

Dackis, C. A., Pottash, A. L. C., Annitto, W., Gold, M. S. (1982) Persistence of urinary marijuana levels after supervised abstinence. Am. J. Psychiat. 139: 1196–1198

Ellis, G. M., Jr, Mann, M. A., Judson, B. E., Schramm, N. T., Tashehian, A. (1985) Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. Clin. Pharmacol. Ther. 38: 572–578

Garrett, E. R., Hunt, C. A. (1977) Pharmacokinetics of delta-9-tetrahydrocannabinol in dogs. J. Pharm. Sci. 66: 395–407

Harvey, D. J., Leuschner, J. T. A., Paton, W. D. M. (1985) Pharmacokinetics of delta-1-tetrahydrocannabinol in the mouse. In: Harvey, D. J. (ed.) Marihuana '84. IRL Press, Oxford, pp 77–84

Hunt, C. A., Jones, R. T. (1980) Tolerance and disposition of tetrahydrocannabinol in man. J. Pharmacol. Exp. Ther. 215: 35–44

Lemberger, L. (1973) Tetrahydrocannabinol metabolism in man. Drug Metab. Dispos. 1: 461–468

Leuschner, J. T. A., Harvey, D. J., Bullingham, R. E. E., Paton, W. D. M. (1986) Pharmacokinetics of Δ^9-tetrahydrocannabinol in rabbits following single and multiple intravenous doses. Drug Metab. Dispos. 14: 230–238

Nahas, G. G. (1984) Toxicology and pharmacology. In: Nahas, G. G. (ed.) Marihuana in science and medicine. Raven Press, New York, pp 109–246

Ohlsson, A., Lindgren, J. E., Leander, K., Agurell, S. (1976) Detection and quantification of tetrahydrocannabinol in blood plasma. In: Willette, R. E. (ed.) Cannabinoids Assay in Humans. NIDA Research Monograph 7, Rockville, pp 48–62

Ohlsson, A., Agurell, S., Lindgren, J. E., Leander, K. (1979) Improvement of mass fragmentographic technique for quantification of tetrahydrocannabinol in human blood plasma. In: Vinson, J. A. (ed.) Cannabinoids Analysis in Physiological Fluids. ACS Symposium Series 98, Washington DC, pp 73–79

Ohlsson, A., Lindgren, J. E., Wahlén, A., Agurell, S., Hollister, L. E., Gillespie, H. K. (1982) Single dose kinetics of deuterium labelled Δ^1-tetrahydrocannabinol in heavy and light cannabis users. Biomed. Mass Spectrom. 9: 6–10.

Peck, C. C., Beal, S. L., Scheiner, L. B., Nichols, A. I. (1984) Extended least squares nonlinear regression: a possible solution to the choice of weight problem in analysis of individual pharmacokinetic data. J. Pharmacokinet. Biopharm. 12: 545–558

Wall, M. E., Sadler, B. M., Brine, D., Taylor, H., Perez-Reyes, M. (1983) Metabolism, disposition and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin. Pharmacol. Ther. 34: 352–363

Widman, M., Halldin, M. M., Agurell, S. (1985) The metabolism of Δ^1-tetrahydrocannabinol in man. In: Barnette, G., Chiang, C. N. (eds) Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs. Biochemical Publications, Foster City, pp 415–426