Short Communication

Urinary Excretion of 11-Nor-9-Carboxy-Δ^9-Tetrahydrocannabinol in a Pregnant Woman Following Heavy, Chronic Cannabis Use

Andreas A. Westin[1,*], Marilyn A. Huestis[2], Kjell Aarstad[1], and **Olav Spigset[1,3]**

[1]Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway; [2]Chemistry and Drug Metabolism, IRP, National Institute on Drug Abuse, National Institutes of Health, Baltimore, Maryland; and [3]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

Abstract

Differentiating new intake of drugs-of-abuse from residual drug excretion may be difficult, especially following chronic drug usage and for drugs with long elimination half-lives such as cannabis. In the present case, cannabis was found in the urine of a young pregnant woman following heavy and chronic cannabis use. She was warned that if she continued using cannabis while pregnant she would be forced to be hospitalized. She was subjected to serial urine testing with 2–7-day intervals. Urinary 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) concentrations, measured by liquid chromatography–mass spectrometry, declined from 348 to 3.9 ng/mL over a surprisingly long period of 12 weeks (84 days). Several algorithms for detecting new drug intake were applied during this time course; most indicated that the woman continued to smoke cannabis following the first urine test. The woman denied any use after the first specimen collection. In retrospect, her THCCOOH excretion profile supports her story. Algorithms for detecting new drug intake have been validated for occasional cannabis users only. We advise caution when interpreting urine test results from heavy, chronic cannabis users, especially when serious consequences are involved.

Introduction

Testing for drugs-of-abuse in urine is often requested in health care, workplace, and criminal justice settings. It is important that results are thoroughly, but also cautiously, interpreted for accurate conclusions to be drawn. For instance, it may be of crucial importance to clinicians and law enforcement to know whether or not there has been new drug intake between two positive specimens from the same individual. However, differentiating new drug use from residual drug excretion may be difficult, especially following chronic drug usage and for drugs with long elimination half-lives such as diazepam (1) and cannabis (2,3).

Δ^9-Tetrahydrocannabinol (THC) is the most psychoactive substance in the cannabis plant. Urine drug screens are designed to detect THC metabolites, primarily 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH). THC metabolites are usually detectable in urine for 1–5 days after a single dose with a 50 ng/mL cutoff (4,5). In chronic cannabis users metabolites may persist for a considerably longer time (6–8). In extreme cases, THCCOOH was reported in urine for 36–95 days after cessation of intake (9–13). Thus, within the time frame of at least three months, a new positive urine specimen does not necessarily imply new cannabis intake. In order to draw such a conclusion, urinary THCCOOH concentrations must be quantified and evaluated.

Although the rate of THCCOOH excretion in urine is relatively constant, its concentration in urine does not continuously decrease with time following cessation of cannabis intake. Hydration effects cause THCCOOH concentrations in urine to fluctuate. Normalizing cannabinoid excretion to the creatinine concentration in urine has been proposed as a tool to overcome this interpretational obstacle (2,3). Because urinary creatinine concentration reflects urine dilution or concentration, dividing urinary THCCOOH concentration by creatinine concentration reduces variability. The urinary THCCOOH concentration/creatinine concentration ratio (CC ratio) makes it easier to distinguish new cannabis use from residual excretion. In theory, following cannabis smoking, the CC ratio should gradually decrease until a new episode of drug use occurs. Manno et al. (2) recommended that in specimens collected at weekly intervals, the CC ratio of the second specimen should be more than 1.5 times the CC ratio of the previous specimen in order to be considered a new drug exposure.

* Author to whom correspondence should be addressed: Andreas Austgulen Westin, M.D., Department of Clinical Pharmacology, St. Olav University Hospital, Olav Kyrres gate 17, N-7006 Trondheim, Norway. E-mail: andreas.westin@legemidler.no.

Huestis et al. (3) investigated CC ratios in occasional users under controlled conditions and found that with the 1.5 decision limit, new drug intake was almost always correctly predicted (0.1% false-positive predictions), but many new intakes were missed (25% false-negative predictions). Huestis et al. (3) suggested that the limit should be 0.5 in occasional users in order to provide the most accurate prediction for new drug use between two specimens. They noted that the Manno approach, a ratio of 1.5 for Specimen 2/Specimen 1 CC ratio, should be used when dealing with cases in which dire consequences could follow identification of new drug use (3).

We present a case in which identification of new cannabis intake by a pregnant Norwegian woman could lead to hospitalization against her will. Norwegian law states that if a pregnant woman is using illicit drugs to an extent that is likely to cause harm to her offspring, social services can decide to institutionalize the woman until childbirth (14). Norwegian law also states that all health personnel are obliged to inform social service whenever they suspect a pregnant woman is endangering her offspring by drug abuse (15). According to the law, this information should be given without considering physician-patient confidentiality. In such cases, pregnant cannabis users are subjected to serial urinary testing and could be institutionalized if continued drug use is determined.

The Case: Initial Circumstances

A Norwegian social service officer suspected that a 20-year-old pregnant female was using illicit drugs. A urine specimen was collected in the 31st week of pregnancy, and it was sent to the Department of Clinical Pharmacology at St. Olav University Hospital for screening for drugs of abuse. It was THCCOOH positive by a liquid chromatography–mass spectrometry (LC–MS) method (described in the Materials and Methods section). She was tested again four and seven days later, still with THCCOOH positive specimens. The woman admitted a history of heavy cannabis use with daily smoking of approximately 5 g of cannabis resin or hashish for several months, including during pregnancy. However, she claimed to have stopped using cannabis after the first cannabinoid-positive specimen. The social service officer needed, in order to execute sanctions, a clear answer from the laboratory: Had she or had she not used cannabis after the first positive specimen? CC ratios declined during the one-week timespan, but the decline was modest. A clear answer could not be given on the basis of these specimens. The social service officer was advised to keep collecting specimens from the patient at several-day intervals throughout the pregnancy.

Materials and Methods

Urinary THCCOOH quantification was performed by positive electrospray ionization LC–MS. In brief, 3.0 mL urine and 0.1 mL THCCOOH-d_3 (4 µg/mL) were treated with β-glucuronidase at 65°C for 60 min, reducing the THCCOOH-glucuronide fraction to less than 5%. Thereafter, THCCOOH was extracted with 6 mL dichloromethane/isopropanol (9:1), the organic phase was evaporated at 40°C, reconstituted in 60 µL methanol/acetonitrile (3:1), and injected on an Agilent MSD 1100 LC–MS system (Agilent, Palo Alto, CA). Separation was performed on a Zorbax Eclipse XDB-C8 (4.6 × 150 mm) column with a methanol/formate-acetate (50:50) mobile phase. The quantification ion for THCCOOH was *m/z* 345.2 with *m/z* 327.2 and 299.3 as qualifier ions. For THCCOOH-d_3, the quantification ion was *m/z* 348.3 with *m/z* 330.2 and 302.3 as qualifier ions. The linear dynamic range was 3.0–1000 ng/mL. Five quality control samples from 5 to 500 ng/mL were analyzed with every batch of unknown specimens. Between-day coefficients of variation (CV) calculated from quality control samples were better than 13.9% at 5 ng/mL and 9.0% at 200 ng/mL

THCCOOH concentrations (in ng/mL) of all positive urine specimens were divided by the specimens' urine creatinine concentration (in mg/mL) to obtain the normalized CC ratio (given in ng/mg). The CC ratio of a positive specimen was then divided by the CC ratio of the previous positive specimen to obtain a between specimen ratio, U. Creatinine was analyzed photometrically after complex formation with picric acid in an alkaline solution by a routine method (Jaffé's method) on a Cobas Integra 400+ multianalyzer (Roche Diagnostics). The limit of quantitation (LOQ) was 0.23 mg/mL with a 3.0% CV. The elimination half-life ($t_{½}$) was calculated by the pharmacokinetic program Kinetica, version 4.3 (InnaPhase, Philadelphia, PA). By using a non-compartment model, the parameter estimate describing the decrease of the log-concentrations (λ_z) was calculated using the best-fit log-linear regression line. The elimination half-life was calculated as $\ln 2/\lambda_z$.

Results

All urine samples were screened for common drugs-of-abuse (e.g., opioids, benzodiazepines, amphetamine, etc.), but only cannabinoids screened and confirmed positive. The first urine specimen voided in the 31st week of pregnancy was collected about 2 weeks after last cannabis intake, according to the client's testimony. It contained 348 ng/mL THCCOOH, and the CC ratio was 110 ng/mg. Further sampling every few days revealed a slow decrease in the CC ratio (Table I, Figure 1). The last positive specimen in the series was collected 12 weeks (84 days) after the first specimen (14 weeks after the alleged last cannabis intake). The urinary THCCOOH concentration in this specimen was 3.9 ng/mL, and the CC ratio was 5 ng/mg. The urinary elimination half-life ($t_{½}$), calculated from CC ratios of 20 urine specimens with THCCOOH concentrations more than the LOQ, was 19.0 days.

Each specimen was assessed by the laboratory for the possibility of new drug use. Four approaches were considered to identify new cannabis use between two consecutive specimens. The one routinely applied by the laboratory was a maximum "CC ratio half-life" of four days (method based on authors' unpublished data from occasional cannabis users). A CC ratio

declining less than expected was considered new intake. This method for the present case suggested new intake for all specimen intervals except one (Table I). Another approach was applying the Huestis method for occasional users (3), expecting the CC ratio to decline by 50% or more whenever specimens were taken more than 24 h apart. Using this approach, all specimens from this client suggested new intake (Table I). A third approach would be to apply a method recently published by Smith et al. (16). In that publication, the original urinary cannabinoid excretion data from Huestis et al. (3) were reanalyzed considering specific timeframes between specimen collections, providing more accurate decreases in creatinine-normalized cannabinoid concentrations for each time interval. Tables were published providing values for expected CC ratio decline in occasional cannabis users based on time between specimens. The tables provide both realistic (based on 95% likelihood) and conservative (based on maximum values) estimates for CC ratio decline with separate tables for THCCOOH concentrations ≥ 15 or ≥ 6 ng/mL. In the present case, the Smith realistic model suggests new intake for all specimen intervals, and the conservative model suggests new intake for all specimen intervals except one (Table I). A fourth approach, the most conservative one, is the Manno method (2), expecting the CC ratio to be lower than 1.5 times the previous positive specimen's CC ratio in specimens taken at weekly intervals. In our case, the between-specimen intervals were often less than a week. Still, applying the specimen ratio of 1.5 as decision limit, none of the specimens would be considered new intake (Table I).

The client was not institutionalized and gave birth to an apparently healthy baby 66 days after the first urine specimen was collected. Thereafter, she was under surveillance by urine monitoring for almost a year with drug-free urine specimens.

Discussion

This case clearly illustrates the challenges of monitoring and interpreting urine cannabinoid concentrations. It raised several crucial questions: What elimination rate should be expected in a heavy cannabis user? How would pregnancy

Table I. Overview of Urine Specimens Obtained From a Woman During and After Pregnancy

Days from First Urine Specimen	Days (Hours) from Prior Specimen	Creatinine Concentration (mg/mL)	THCCOOH Concentration (ng/mL)	CC Ratio* (ng/mg)	CC Ratio Half-Life† (days)	U‡	Interpreted as New Cannabis Intake after Previous Specimen? 4 days' half-life method	Huestis model (U > 0.5)	Smith model (realistic)§	Smith model (conservative)§	Manno model# (U > 1.5)
0	–	3.2	348.1	110.3	–	–	–	–	–	–	–
4	4 (96)	2.0	139.9	69.5	6.0	0.6	Yes	Yes	Yes	Yes	No
7	3 (72)	1.1	101.1	90.3		1.3	Yes	Yes	Yes	Yes	No
12	5 (120)	1.6	91.2	58.0	7.9	0.6	Yes	Yes	Yes	Yes	No
14	2 (46)	1.9	139.0	73.6		1.3	Yes	Yes	Yes	Yes	No
18	4 (96)	2.3	135.0	59.1	12.6	0.8	Yes	Yes	Yes	Yes	No
21	3 (72)	2.0	81.9	41.9	6.0	0.7	Yes	Yes	Yes	Yes	No
25	4 (96)	2.2	121.0	55.7		1.3	Yes	Yes	Yes	Yes	No
28	3 (71)	1.2	42.9	35.1	4.5	0.6	Yes	Yes	Yes	Yes	No
32	4 (96)	1.9	79.4	42.3		1.2	Yes	Yes	Yes	Yes	No
39	7 (167)	1.4	46.8	33.6	21.1	0.8	Yes	Yes	Yes	Yes	No
42	3 (74)	1.0	29.4	28.6	12.9	0.8	Yes	Yes	Yes	Yes	No
46	4 (95)	1.2	30.8	25.9	28.0	0.9	Yes	Yes	Yes	Yes	No
49	3 (72)	1.2	28.2	22.9	16.9	0.9	Yes	Yes	Yes	Yes	No
53	4 (96)	1.1	21.3	19.4	16.7	0.9	Yes	Yes	Yes	Yes	No
56	3 (72)	2.2	24.7	11.3	3.8	0.6	No	Yes	Yes	Yes	No
61	5 (121)	3.5	24.0	6.8	6.8	0.6	Yes	Yes	Yes	Yes	No
63	2 (49)	2.3	20.9	9.2		1.4	Yes	Yes	Yes	Yes	No
66**	3										
81	18 (432)	1.7	10.5	6.1	30.4	0.7	Yes	Yes	Yes	Yes	No
84	3 (75)	0.8	3.9	5.0	10.5	0.8	Yes	Yes	Yes	No	No
88	4 (96)	< 0.23	Not detected	–	–	–	–	–	–	–	–

* CC ratio is the urinary THCCOOH concentration divided by the creatinine concentration.
† CC ratio half-life calculated from the last two (i.e., the previous and the present) specimens. Blank spaces indicate increasing CC ratio value from previous specimen (thus, half-life cannot be calculated).
‡ U is the CC ratio of the present specimen divided by that in the previously collected specimen.
§ The Smith model provides realistic (based on 95% likelihood) and conservative (based on maximum values) estimates for CC ratio decline between two specimens. The estimates depend on whether cannabinoid concentrations equal to or greater than 6 or 15 ng/mL are employed and take into consideration the collection intervals between urine specimens. The 95% likelihood and conservative limits based on maximum values for specific collection intervals are taken directly from tables in the article (16).
# The Manno model suggests that specimens should be collected at weekly intervals. In the present case, the collection intervals were often shorter than this. Still, no specimen ratios exceeded the U > 1.5 limit.
** The woman gave birth on day 66. No specimen was collected.

influence cannabis pharmacokinetics? How often should specimens be obtained and interpreted? How long is it ethical to wait before advising social services to take action considering the fact that the client could still be smoking cannabis while pregnant?

In the present case, THCCOOH was detected in the woman's urine for 84 days after the first specimen collection, and the calculated urinary elimination half-life ($t_{½}$) of the CC ratio was 19.0 days. Similar findings have previously been described by Lafolie et al. (11) and Smith-Kielland et al. (12), who have reported CC ratio half-lives of 32 and 16 days, respectively, in single cases of heavy, chronic cannabis use. Given the consequences at stake and the client's history of heavy cannabis use, the overall conclusion from the laboratory was that the slowly falling slope of the CC ratio curve (Figure 1) was a result of residual THCCOOH excretion and not of recent intake(s). However, we are well-aware that this violated our method for the interpretation of new cannabis intake based upon two consecutive samples.

Objective criteria are needed for the interpretation of an individual's CC ratio over time in chronic cannabis users in order to differentiate new cannabis use from residual excretion. The specimen ratio (the CC ratio of the latter specimen divided by that of the previous specimen) has been suggested as useful for this purpose (2,3). A specimen ratio of 1.5 has been commonly used for chronic cannabis users (17–20), although empirical data indicated that this limit was too conservative for occasional cannabis users, where a specimen ratio of 0.5 provided more accurate results (3). A recent work allows for more detailed interpretation, taking into account the exact times between specimen collections (16). However, none of the studies were validated for use on data from heavy, chronic cannabis users. Applying interpretations derived from occasional users to heavy cannabis users may increase the risk of erroneously concluding new drug intake.

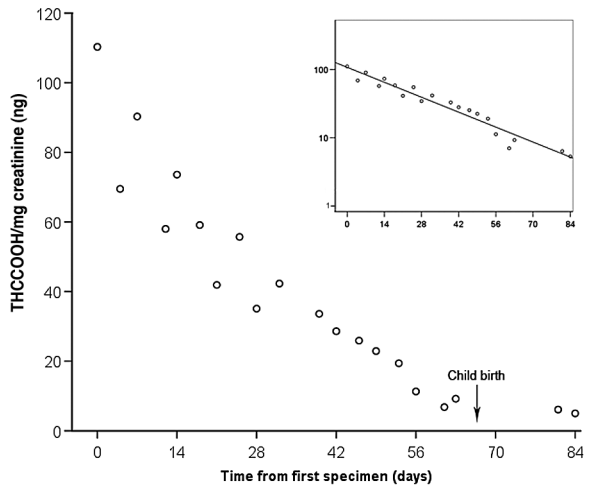

Figure 1. Ratios of urinary 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) concentrations (ng/mL) to creatinine concentrations (mg/mL) (CC ratios) in a pregnant woman following heavy intake of cannabis. The first specimen (Day 0 on the x-axis) was collected on the 31st week of pregnancy. The client gave birth 66 days later. Each specimen is represented by a circle. The small box shows the same plot with a logarithmic ordinate and the best-fitting regression line, indicating the elimination half-life.

Another aspect that needs attention is the fact that the woman was pregnant. Multiple physiologic changes occur during pregnancy and may influence cannabinoid pharmacokinetics. Alterations in the plasma volume and the volume of distribution for drugs, altered drug protein binding, changes in metabolic capacity, and increased renal blood flow with enhanced glomerular filtration rate are all important factors known to alter the pharmacokinetic properties of drugs during pregnancy (21). The effect of pregnancy on the pharmacokinetic properties of cannabinoids is not known, and the subject is scientifically challenging to investigate for obvious ethical reasons. Thus, we do not know whether urinary cannabinoid excretion changes during pregnancy, and if so, if it is increased or decreased. However, we do know that the absolute and relative amounts of body fat increase during pregnancy (22). One may speculate that a larger amount of body fat may increase the storage capacity for cannabinoids in pregnant users compared to non-pregnant users. This may, at least in theory, lead to an extended cannabinoid excretion time in pregnant subjects. Regarding THC elimination, the rate-limiting step is redistribution from tissue deposits back into the circulation (23), to our knowledge, a factor that has not yet been evaluated in pregnancy.

Pregnancy adds to the complexity of interpretation. It also adds to the importance of an accurate judgment regarding new intake. In the present case, a false-positive judgment of new intake could result in the woman, although innocent of new drug use, being institutionalized against her will in an addiction treatment clinic. On the other hand, a false-negative judgment would imply that the mother was still using cannabis and that the unborn child was repeatedly exposed without the laboratory being able to report it. Thus, there would be dire consequences either way.

Although we do not know with certainty, we have reason to believe that the client abstained from cannabis use after the first specimen was collected. In the process of writing this article, the authors discretely contacted the client through a written letter, in which she was given the opportunity to contact the laboratory if she was interested in telling her version of the story. In the letter, she was informed that if she did not contact us, we would not contact her again, and the social service would not be informed in any case. She contacted us the same week the letter was sent and maintained that she had not been smoking after the first specimen was taken. She was grateful to be believed by medical staff and agreed that publishing her story might shed light on a matter of importance for others in her situation.

Conclusions

We present data on the elimination time of THCCOOH in a pregnant woman following long-term heavy cannabis use. The final conclusion by laboratory medical staff was that there had

not been new cannabis intake after the first specimen. Assuming that this is the correct conclusion, the conservative approach suggested by Manno et al. (2) would be the most accurate for this situation. It is unknown whether pregnancy alters cannabinoid pharmacokinetics; however, it is known that heavy cannabis use may lead to prolonged excretion of THC metabolites. The present case illustrates a rather extreme situation, a pregnant woman having smoked 5 g of hashish daily for several months. We have one subject only and cannot define an exact algorithm for interpreting these specimens. However, we advise following up on such cases by sampling urine frequently, interpretating results carefully, and monitoring the declining slope of the CC ratio until cannabinoids are no longer detectable.

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