Urinary Excretion of 11-nor-9-Carboxy-Δ⁹-
Tetrahydrocannabinol and Cannabinoids in
Frequent and Infrequent Drug Users*

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Abstract

Urinary excretion of 11-nor-9-carboxy-Δ⁹-tetrahydrocannabinol (THCCOOH) and cannabinoids was monitored in prison inmates. Urinary specimens were collected up to five times per day. EMIT™ (cutoff 20 ng/mL; EMIT20) and gas chromatography (GC) (cutoff 10.3 ng/mL, LOD 1.4 ng/mL) were used for cannabinoid screening and THCCOOH confirmation, respectively. Urinary creatinine concentrations were recorded. Of the samples with positive EMIT screens, 78% were confirmed by GC analysis. The plotting of THCCOOH/creatinine ratios (THCCOOH/C) versus time gave smoother excretion curves than THCCOOH concentrations alone. Based on THCCOOH/C the first 5 days after the last reported intake, the mean urinary excretion half-life was 1.3 days in infrequent users, and a median of 1.4 days was found in frequent users. In the latter group, apparent terminal urinary excretion half-lives up to 10.3 days were observed. The last positive specimens were found after 4 days for THCCOOH with cutoff 15.0 ng/mL (NIDA/SAMSHA), 5 days for THCCOOH with cutoff 10.3 ng/mL, and 12 days for cannabinoids (EMIT20) in infrequent users and after 17, 22, and 27 days, respectively, in frequent users. Increases in urinary cannabinoids were sometimes found without concomitant increase in THCCOOH or THCCOOH/C. One subject admitted new cannabis intake, after which marked increases in THCCOOH and THCCOOH/C were observed. In others, new intake was suspected. Considerable variations between consecutive specimens were also observed in THCCOOH concentration and THCCOOH/C ratio without suspicion of a new intake.

Introduction

Cannabis (hashish/marijuana) is the most frequently used illegal drug in Norway, as judged from drug-use survey questionnaires (1) and from the results of about 30,000 urine samples analyzed annually at the National Institute of Forensic Toxicology. In spite of the high frequency of use, few controlled studies on kinetics of urinary excretion have been published. Huestis et al. (2,3) followed the urinary excretion of cannabinoids and the main urinary metabolite 11-nor-9-carboxy-Δ⁹-tetrahydrocannabinol (THCCOOH) for a week after intake of a single smoked dose. Detailed long-term studies with frequent collection of urinary specimens to follow the urinary excretion after chronic intake of cannabinoids appear to be needed. For ethical reasons, such studies cannot be done on healthy volunteers. Technically, long-term studies require extended periods of urine collection, demanding considerable personnel and economic resources. Strategies to lower the number of samples and costs have been collecting urine specimens into 12- or 24-h pools, shortening the period of collection, collecting only early-morning urine, or combinations of these measures (4–13). However, in real-world situations, a single specimen is collected at any hour. Interpretation with respect to previous drug use often has to be made on the basis of this single or a few test results. Urine sampling may be carried out for a number of reasons, such as follow-up on a subject during imprisonment, during a drug-treatment program, parole and probation monitoring, employee-rehabilitation programs, or for workplace drug testing. The crucial question is usually whether a positive specimen represents a recent, previously not registered intake.

Often, the variability in urine production, which depends on the hydration status of the subject, makes interpretation difficult. Urinary creatinine concentration has been suggested as a useful correction factor for variable urine dilution in the study of cannabinoid as well as THCCOOH excretion (2,14). It was therefore of interest to compare the variations in THCCOOH concentration in consecutive specimens with the THCCOOH concentration related to creatinine (THCCOOH/C) in the same specimen. This investigation presents urinary excretion profiles of THCCOOH and the ratio of THCCOOH/C in drug users. Urinary specimens were collected up to five times daily until urine became negative as measured by EMIT20 screening. Gas chromatography (GC) was used for analysis of THCCOOH concentrations. Detection times and other excretion parameters were determined. Several participants withdrew from the study, and new cannabis intake was observed within the experimental period.

* Parts of this work were presented at the 31st Meeting of The International Association of Forensic Toxicologists (TIAFT), Leipzig, Germany, 1993; at the First European Symposium on Drug Testing at Workplace, Stockholm, Sweden, 1998; and at the SOFT-TIAFT meeting, Albuquerque, NM, 1998.

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Methods

Participants

Drug users were recruited over a three-year period, 1991–1994, when they started to serve their sentence in the prison of Trondheim, Norway (population, approximately 140,000). There was never more than one participant in the study at a time. The participants answered a questionnaire concerning their drug habits (not available to prison authorities), including duration of drug abuse, the frequency of drug intake, which drugs they used, and the time of their last drug intake. In addition, the participants were asked to mark in a table how often they used the various drugs of abuse. Some inconsistencies were observed. Frequently, only the date and not the time of the last intake was given. In those cases, intake was set to 12 p.m. The time of imprisonment was also set at noon at the day the sentence started unless otherwise stated. Participants did not always enroll into the program the first day of imprisonment. Medication obtained by prescription during imprisonment was noted. The participants were housed together with other prison inmates and were not under continuous surveillance. Participants told the prison staff there was strong pressure from fellow inmates not to participate in the study in order to avoid cooperating with "the authorities". The participants were assigned an arbitrary alphabetical letter to conceal their identities as far as possible.

The cannabis users were divided into two groups based on the information given in the questionnaire. Infrequent users reported cannabis intake less than once weekly, and frequent users reported mostly daily use. However, last intake was sometimes noted to be some days before imprisonment.

The only female participant was grouped with the males because no difference between men and women in the kinetics of urinary excretion of THCCOOH has been reported (6).

Ethics

Written informed consent was obtained, and the subjects could withdraw at any time during the testing period, as required by the Declaration of Helsinki. The prison management had agreed not to be informed of the analytical results. The results of the tested urine specimens were confidential. There was no cross-reference between the National Institute of Forensic Toxicology (NIFT) database and the database of the present study. In an attempt to prevent the testing period from being a shield from prison restrictions and thus open for new drug intakes, the protocol allowed for prison inspectors to collect additional "routine" urine specimens. Action could be taken according to the results of the subsequent "routine" analysis and interpretation from the NIFT. However, prison inspectors never suspected new intakes (personal communication). The participants received compensation for each specimen (approximately $5.00). The study protocol was approved by the Ethics Committee of Health Region 2, the Norwegian Data Inspectorate, and the Board of Professional Secrecy and Science.

Urine sampling

Subjects yielded a urine specimen 1–5 times daily. The prison inspectors decided the time of collection. Rigorous chain-of-custody procedures were followed. Urine collection was performed under strict surveillance. The testing period was terminated after the evaluation of screening results from the individual participants. The number of screening negatives late in the collection period tended to increase as experience expanded throughout the three-year study. The specimens were kept in polyethylene vials refrigerated at 4–8°C until sent by mail; specimens were normally received the next day at NIFT in Oslo. The urine was kept refrigerated until screening was performed and then normally stored at −18°C.

Chemicals

RTI (Research Triangle Park, NC) supplied the 11-nor-Δ⁹-THC-COOH standard, and 11-nor-Δ⁸-THCCOOH was the internal standard. Deuterated 11-nor-Δ⁹-THCCOOH-d₃ (Radian Corp., Austin, TX) was used as internal standard for gas chromatographic–mass spectrometric (GC–MS) analyses. All solvents and reagents were of reagent grade.

Urine analyses

All samples were analyzed at NIFT by immunological screening by polyclonal cannabinoid EMIT® d.a.u. or monoclonal EMIT® II (from 1993 onwards) with 20-ng/mL cutoff assays (denoted EMIT20) from Syva Co. (now Dade-Behring Diagnostica). No major difference in screening positives could be detected between the two EMIT kits by direct comparison of a limited number of specimens or by statistical evaluation of the number of screening positives in 1992 compared with 1993 (around 7% cannabis positives out of 17,000–20,000 urine specimens). The samples were analyzed on a Monarch 2000 Chemistry system (Instrumentation Labs, Lexington, MA) operating at 30°C.

The system was run in the semiquantitative mode with calibrators at 0, 20, 35, and 50 ng/mL and with positive and negative controls. Values above the high calibrator were usually reported as such (greater than highest calibrator) and denoted 50 ng/mL in further calculations. The coefficient of variation (CV) of the spiked positive control (40 ng/mL) was 18%, and the CV of the cutoff calibrator was 15% (EMIT II reagents) in this system. In comparison, the cutoff practiced by NIDA/SAMSHA is 50 ng/mL.

Figure 1. Scattergram of urinary cannabinoid EMIT screening values (20-ng/mL cutoff, highest calibrator 50 ng/mL) as a function of THCCOOH concentration up to 100 ng/mL.
for the immunological screening assay.

Urinary creatinine was analyzed by the alkaline picrate method (IL test™, Instrumentation Laboratories, Milan, Italy) with a CV of 6% at a creatinine concentration of 10 μmol/mL (1 μmol/mL = 11.3 mg/dL). In all samples pH was measured with a pH meter (Beckman pH 10) or with indicator paper (Neutralit® pH 5–10, Merck, Darmstadt, Germany).

**GC confirmation**

THCCOOH confirmation was carried out on all specimens that screened positive and on 428 out of 612 EMIT20-negative specimens. THCCOOH was measured in 1.0 mL urine according to the method of ElSohly et al. (15) with minor modifications using a fused-silica capillary column (SPB™-35, 15 m × 0.32-mm i.d., 0.25-μm film thickness, Supelco, Bellefonte, PA) installed in a Hewlett Packard (Palo Alto, CA) 5880 GC with an electron capture (EC) detector. The retention time window was set to 0.5%. The limit of detection was 1.4 ng/mL, the cutoff was 10.3 ng/mL, and the CV was 14% at a concentration 20% above the cutoff. Storage for three months at −20°C did not change the THCCOOH concentration of spiked samples (range 10–200 ng/mL). A repeated freeze/thaw process (five times during one week on spiked samples containing 10–30 ng/mL) was found to lower the THCCOOH concentration by up to 15% as tested by this method.

In authentic samples the reduction by the same freeze/thaw procedure was found to be 10% measured by GC-MS.

Several of the participants were urine positive for more than one drug. Specimens from these subjects (up to two weeks after imprisonment) were therefore frozen/thawed more than once. The majority of the specimens were thawed and analyzed in duplicate within three months (subjects B–F1, G, L, M, P, R, S, U, W), although singular specimens were sometimes reanalyzed at a later stage. The rest were analyzed within a year. In some instances, large concentration differences were observed between consecutive specimens. A few of these (from the same subject) were reanalyzed by GC–MS after three years (thawed twice), the results being up to 25% lower, but the concentration differences between consecutive specimens were consistent with the previous GC analysis. The GC–MS method used pentafluoropropionic acid anhydride (PFPA) for derivatization, and an HP 5890 with a 5970 MSD was run in the selected ion monitoring mode. The limit of detection was 3.8 ng/mL, and the CV was 15%. The results of the two confirmation methods has been reported to correspond satisfactorily (16) as did comparison of selected samples in our lab. From April 1993, all NIFT routine THCCOOH confirmation analyses were run on GC–MS, and the fraction of confirmed positives were similar when comparing the two methods. GC–MS analyses were not performed on all specimens because of the lack of a validated method at the start of the study and the lack of instrument capacity later on.

The NIDA/SAMSHA cutoff is 15.0 ng/mL.

**Graphic presentations and data analyses**

The xy scattering plot (Figure 1) of screening results versus confirmation results was analyzed by linear regression using Excel (version 5.0, Microsoft, Redmond, WA). The starting point of the individual excretion curves was based on the self-reports of the last intake. The THCCOOH concentration curves as well as curves defined by the ratio THCCOOH/C were tested with regard to first order kinetics in semilogarithmic plots using Freelance Graphics (version 4.0, Lotus Development Co., Cambridge, MA) and the general equation \( y = ae^{−bx} \) (compare to \( C = C_0e^{−kt} \)). A regression line was used to sets of data points, calculating the correlation coefficient \( r^2 \). The apparent urinary excretion half-life is given by the equation \( t_{1/2} = 0.693/k \) (17). For all subjects, the \( t_{1/2} \) was estimated for the first five days after last reported intake. The equation is not accurate for drugs distributing according to multicompartiment models. However, it was used together with visual inspection to describe the various parts of the curves. Concentrations of THCCOOH below the limit of detection (1.4 ng/mL) were denoted as 0 in the calculations, but for technical reasons, were marked as 1 ng/mL THCCOOH and 0.1 ng/μmol THCCOOH/C in Figures 2–4.

**Results**

Twenty-two drug abusers (21 men and 1 woman) agreed to participate during the three-year project period. One male (F) participated twice (denoted F1 and F2) within a one-year interval. All subjects reported use of cannabinoids, but two...
Figure 3. Frequent users. Each curve shows the urinary concentration of THCCOOH (nanograms per milliliter, upper curve) and the THCCOOH concentration related to the creatinine concentration (micromoles per milliliter) of each specimen (THCCOOH/C ratio, nanograms per micromole, lower curve) as a function of days after self-reported intake. THCCOOH values below the limit of detection (LOD) were denoted as 0 in the calculations, but were denoted as 1 in the figures for technical reasons, and the corresponding THCCOOH/C ratios were denoted 0.1. THCCOOH cutoff (10.3 ng/mL, ---) and LOD (1.4 ng/mL, - - -) are marked in each figure. The regression line(s), coefficient(s) ($r^2$), and corresponding $t_{1/2}$ are shown.
tested negative. These two reported their last cannabis intakes 8 and 86 days before imprisonment. One subject submitted only two samples before withdrawing and was not included. Of the 19 participants included, 8 withdrew from the study before the testing period was terminated (A, E, F2, H, I, K, M, and S). Two of these subjects withdrew because they were released from prison. Most of the subjects reported themselves to be multidrug users. Benzo-diazepines were found in urine from 8 subjects, amphetamines from 7 subjects, and opiates from 4 subjects out of the 19 subjects included. In five subjects, three different drugs were found at the start of imprisonment. Some of the subjects did not report all the compounds found in their urine samples, and others reported intake of compounds that were not found. One frequent user (L) reported daily intake of cannabinoids but a last intake 8 days before imprisonment, and other inconsistencies regarding other drugs. Generally, the reported amount of the drug at the last intake could not be transformed into doses actually taken by the subjects. Table I lists the median age, weight, height, and body mass index of the infrequent and frequent users. Subject H reported intake up to four times monthly taking only "some puffs" at the last

Figure 3 (continued). Frequent users. Each curve shows the urinary concentration of THCCOOH (nanograms per milliliter, upper curve) and the THCCOOH concentration related to the creatinine concentration (micromoles per milliliter) of each specimen (THCCOOH/C ratio, nanograms per micromole, lower curve) as a function of days after self-reported intake. THCCOOH values below the limit of detection (LOD) were denoted as 0 in the calculations, but were denoted as 1 in the figures for technical reasons, and the corresponding THCCOOH/C ratios were denoted 0.1. THCCOOH cutoff (10.3 ng/mL, — — —) and LOD (1.4 ng/mL, - - -) are marked in each figure. The regression line(s), coefficient(s) (r²), and corresponding t1/2 are shown.
intake; he was evaluated separately (Figure 4). His age, weight, and height were 31 years, 70 kg, and 1.65 m, respectively.

Cannabis screening
In total 1432 urine specimens were received and screened by EMIT20, and 1248 of these were analyzed by GC. There were 820 EMIT20 positives, and 638 (78%) of these were confirmed as THCCOOH positive. Out of the 428 EMIT20 negative specimens analyzed by GC, 7 specimens were positive by THCCOOH confirmation. Applying the NIDA/SAMSHA confirmation cutoff (15.0 ng/mL) would have reduced the number of confirmed THCCOOH positives by 137 (22%). Figure 1 shows the relationship between urinary THCCOOH concentration up to 100 ng/mL and EMIT20 values. There appeared to be no linear relationship between the two types of results.

### Table I. Age, Weight, Height, and Body Mass Index of the Cannabinoid/Positive Participants*

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Body mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infrequent users</strong> (n=4)</td>
<td>30 (19–33)</td>
<td>80.5 (60–97)</td>
<td>1.85 (1.72–1.92)</td>
<td>22.3 (19.8–29.9)</td>
</tr>
<tr>
<td><strong>Frequent users</strong> (n=14)</td>
<td>29.5 (16–38)</td>
<td>68.5 (60–75)</td>
<td>1.75 (1.58–1.94)</td>
<td>21.8 (19.7–25.7)</td>
</tr>
</tbody>
</table>

* Median values and ranges are given.

Infrequent users
Four male subjects reported infrequent use. One of these reported last intake four days before imprisonment. He had from the start of the testing period three consecutive screening positive specimens, and the following 25 were screening negative. Of these, the first seven samples were analyzed for THCCOOH, none of which were positive. The results from this subject were not included in the analysis of the other characteristics of excetration. For the other three subjects, there was a median time from last reported intake to imprisonment of one day (range 0.5–3 days). Included in the group of infrequent users were also the results from one of the frequent users (subject M, Figure 3). He had a new intake late in the testing period when he had been screening and confirmation negative for five days (21 days after intake).

Figure 2A shows the individual THCCOOH concentration excretion curves, and Figure 2B the THCCOOH/C ratios. The THCCOOH/C curves were smoother than the corresponding THCCOOH curves (r² = 0.87 for THCCOOH/C versus r² = 0.55 for THCCOOH) based on pooled data from day 0 to 5 after reported intake. The THCCOOH/C regression line was described by the equation \( y = 15.3e^{-0.87x} \), giving an estimated mean half-life of 1.3 days (range 0.74–1.5 days). In no instance was there any major increase in the THCCOOH/C ratio, which would indicate a new intake of cannabis in this group. Even from five days onwards there were low but detectable concentrations of THC-COOH in most of the specimens analyzed.

Some characteristics regarding cannabinoid (EMIT20) and THCCOOH excretion such as detection times, the number of negative gaps (fluctuations from positive to negative, and then positive specimens), and the lengths of the longest gaps are shown in the upper part of Table II.

### Table II. Urinary Excretion of Cannabinoids and THCCOOH in Frequent and Infrequent Users*

<table>
<thead>
<tr>
<th></th>
<th>After intake*</th>
<th>After imprisonment</th>
<th>No. of negative gaps (n)</th>
<th>Longest negative gaps (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Last positive</td>
<td>First negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infrequent users</strong> (n = 3–4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabinoids (cutoff 20 ng/mL)</td>
<td>12.3 (4.5–14.3)</td>
<td>10.8 (1.0–13.8)</td>
<td>3.8 (1.1–5.0)</td>
<td>3 (0–8)</td>
</tr>
<tr>
<td>THCCOOH (cutoff 10.3 ng/mL)</td>
<td>5.3 (4.5–5.4)</td>
<td>3.8 (1.0–4.9)</td>
<td>3.2 (1.1–4.0)</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>THCCOOH (cutoff 15.0 ng/mL)</td>
<td>4.2 (3.3–4.5)</td>
<td>2.6 (1.0–4.0)</td>
<td>2.8 (1.0–3.3)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td><strong>Frequent users</strong> (n = 9–14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabinoids (cutoff 20 ng/mL)</td>
<td>26.5 (8–32)</td>
<td>25.0 (5–31)</td>
<td>113 (2–25)</td>
<td>5.5 (2–12)</td>
</tr>
<tr>
<td>THCCOOH (cutoff 10.3 ng/mL)</td>
<td>22.4 (5–30)</td>
<td>19.4 (4–28)</td>
<td>8.7 (3–24)</td>
<td>5.5 (0–16)</td>
</tr>
<tr>
<td>THCCOOH (cutoff 15.0 ng/mL)</td>
<td>16.6 (4–28)</td>
<td>14.1 (1–26)</td>
<td>5.8 (1–21)</td>
<td>4 (0–13)</td>
</tr>
</tbody>
</table>

* Median values and range are given. Suspected new intakes are not included. In some cases, first negative specimen could have taken place before imprisonment and the last positive after the testing period was ended; when reasonable doubt was present, these data were not included.

* According to self-report.
Frequent users

Thirteen users were included in the group; one represented on two occasions (subject F). Median time from last reported intake to imprisonment was two days (range 0–8 days). In Figure 3, the individual urinary excretion curves are shown with regard to THCCOOH concentration and THCCOOH/C ratio. The THC-COOH/C ratio gave smoother curves than the THCCOOH concentration curves, as judged from visual inspection and regression line coefficients (higher $r^2$ values, comparison not shown), showing that creatinine would correct for much of the variation between consecutive specimens. Several of the curves were quite complex, consisting of at least two phases. The median apparent urinary excretion half-life during the first five days after reported intake was 1.4 days (range 1.0–2.3 days). There seemed to be an intermediary urinary excretion half-life of 3.9 days (range 3.0–4.6 days) in some of the subjects from day 5 after last intake and up to around 16 days (Visual inspection, assuming subject L was not correct in his report concerning last intake. See Participants). In several of the subjects an even longer terminal urinary excretion half-life based on the THCCOOH/C ratio was found from five days onwards the median value being 7.1 days (range 6.3–10.3 days, details in Figure 3). Close inspection of some of these curves might indicate a composite of two curves with a shorter and a longer half-life. The last part of curve of subject I (Figure 3) from day 16 to 28 had a $t_{1/2}$ of 12.7 days and a low $r^2$ of 0.25.

The veracity of some of the participants’ self-reports may be doubted. Judging from the high THCCOOH concentration at the start of testing and the time curve of subject L, it seems unlikely to be as much as eight days between last reported intake and first specimen taken. Subject H claimed to be an infrequent user taking only a few puffs at the last intake. However, his excretion curve (shown in Figure 4) resembles some of the frequent user curves as shown in Figure 3.

In some of the subjects, several screening-negative specimens were followed by positive specimens late in the testing period, indicating a new intake. However, on some occasions, there was no simultaneous increase in the THCCOOH concentrations or THCCOOH/C ratios (Figure 5).

Detection times and other urinary excretion characteristics of cannabinoids (EMIT20) and THCCOOH concentrations are shown in the lower part of Table II. The median of the first negative as well as the last positive cannabinoid and THCCOOH results appeared several days later in the frequent users than in the infrequent users.

In the frequent user group the number of fluctuations between negative and positive specimens (i.e., negative gaps) were higher, and the longest negative gaps were of longer duration. The urinary excretion of subject I was most extraordinary with 12 and 16 negative gaps with regard to EMIT20 screening and THCCOOH concentration, respectively (not including the period of day 28–35 of suspected new intake). It was observed that her urine specimens with high or low creatinine concentration, gave correspondingly high or low THCCOOH and EMIT20 concentrations (data not shown) thus, to a large extent, accounting for the negative gaps.

The longest negative gap with respect to THCCOOH concentration of 6.2 days was observed in the female subject I (Figure 3) between day 28 and day 34 after last reported intake. Twenty-three negative specimens were collected before a new positive appeared. Within that same period there were six positive EMIT20 specimens (data not shown). Subject I was also extreme in having 28 out of 123 collected urine specimens (23%) with creatinine concentrations below 3.0 μmol/mL (33.9 mg/dL). Some subjects being under prison restrictions might have a high fluid intake because of their confinement. However, a deliberate forcing of fluid intake to decrease the risk of detection of new drug intake cannot be ruled out.

Details concerning actual concentrations of THCCOOH and THCCOOH/C ratios shortly after an intake have been of interest in the interpretation of analytical results. Table III shows some observations at the time of imprisonment as well as 24 h and 48 h thereafter.
In most Norwegian prisons, there is access to drugs in spite of various countermeasures by the prison management. Based on the analytical results and inspection of the curves, new intakes were suspected in the subjects A, F2, G, I, and M (Figure 3). After release from prison, subject M admitted a new intake during the testing period. The data showed a THCCOOH concentration below the limit of detection in the evening 20.8 days after intake, and the next morning the urinary concentration was 132 ng/mL. The THCCOOH/C ratio was 0.4–0.5 ng/µmol in the last 5 specimens with detectable THCCOOH concentration before the new intake, and the ratio rose to 11.8 ng/µmol afterwards. The apparent elimination half-life (day 21–28) was 1.3 days (r² = 0.91) compared to 7.3 days for the period preceding the new intake. Subject A withdrew from the study right after a suspected new intake on day 14. However, the increases in both THCCOOH concentration (from 10.7 to 107 ng/mL between consecutive specimens) and the corresponding THCCOOH/C ratio (0.8 to 11.6 ng/µmol) were substantial. Subject G had a marked rise both with regard to the THCCOOH concentration (8.2 to 96 ng/mL) and THCCOOH/C (0.9 to 7.6 ng/µmol) between day 15 and 16. There was a calculated t₁/₂ = 0.7 (r² = 0.89, Figure 3) for the period 16–18 days compared to 4.3 days for the preceding period. Subject I, at around day 28, passed from a negative THCCOOH (3.1 ng/mL) in the evening to a positive concentration (31 ng/mL) the next morning, followed by another negative (10.0 ng/mL) 4.3 h later. During the next 6.2 days, the THCCOOH concentrations were below the cutoff (10.3 ng/mL) after which a new THCCOOH positive specimen (12 ng/mL) was observed, followed by two negative specimens. The fivefold increase in THCCOOH/C ratio (from 0.9 to 4.4 ng/µmol) could indicate, more strongly than the THCCOOH concentration itself, a new intake. Calculations based on specimens from day 28–30 (n = 9) gave an apparent urinary excretion half-life of 0.7 days (r² = 0.80) compared with 7.6 days for the preceding period. During the next four days, there were several screening and confirmed positive specimens, but the THCCOOH/C ratios were all below 2 ng/µmol. On some occasions, similar increases in the THCCOOH/C ratio was observed from one specimen to the subsequent specimen without apparent new intake as judged from inspection of the curves.

### Discussion

There are limitations included in the present study. The participants themselves supplied information about their drug use. This is a notoriously unreliable source. The information was not detailed enough for calculation of doses taken, etc. The participants were on a waiting list to serve their sentences and were summoned on a fixed date. This may have caused changes in the frequency and intensity of drug use in the days or weeks before imprisonment.

Even though urine specimens were collected every day (up to 127 specimens for 38 days), sampling of every void did not take place. This fact could change the timing of first negative and last positive specimens and duration of negative gaps.

<table>
<thead>
<tr>
<th>Subject</th>
<th>First urine specimen (2–3 h after imprisonment)</th>
<th>About 24 h after first specimen</th>
<th>About 48 h after first specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>THCCOOH (ng/mL)</td>
<td>THCCOOH/C (ng/µmol)</td>
<td>THCCOOH (ng/mL)</td>
</tr>
<tr>
<td>Infrequent users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>132</td>
<td>11.8</td>
<td>33.4</td>
</tr>
<tr>
<td>B</td>
<td>148</td>
<td>9.0</td>
<td>41.0</td>
</tr>
<tr>
<td>Frequent users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>94.4</td>
<td>8.5</td>
<td>35.5</td>
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<tr>
<td>F1*</td>
<td>266</td>
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<td>255</td>
</tr>
<tr>
<td>F2*</td>
<td>483</td>
<td>31</td>
<td>646</td>
</tr>
<tr>
<td>S</td>
<td>888</td>
<td>44</td>
<td>340</td>
</tr>
</tbody>
</table>

* Last intake was reported to be 10–48 h before the first collected specimen.
† First sample after a new intake within prison.
* F1: the first testing period of subject F. Last intake was reported 20 h before imprisonment and a peak urinary concentration of 346 ng/mL was observed 20 h after the first specimen.
* F2: the second testing period. Peak urinary concentration of 650 ng/mL was observed 4 h after first specimen.
The participants were not specifically asked to report to the investigators new drug intakes during the excretion study. Although no consequences were to follow such reports, the inmates might not have been confident about this, and accordingly reluctant to report.

An extended period of time passed from screening until confirmation analyses were performed in several subjects, possibly giving somewhat lower concentrations of THCCOOH than originally present. The number of confirmed screening positive specimens observed during routine analyses at NIPT in the same period was 80–85% as compared with 78% in the present study.

The number of participants in the infrequent user group was quite limited.

In spite of the shortcomings, the presented data illustrate the genuine excretion of cannabinoids as a function of time in drug users. Even though urine sampling from prison inmates is no standard pharmacokinetic sampling method, the data suggested a mean urinary excretion half-life in infrequent users of 1.3 days for THCCOOH as measured the first five days after intake, and a similar median half-life in frequent users (1.4 days). This agrees quite well with other studies (6,13) and supports previous findings of no major difference in the excretion kinetics of frequent and infrequent users in the initial phase after intake. Moreover, profiles of the excretion curves in the two groups were sufficiently different to doubt the self-report of subject H. His excretion curve was hardly compatible with the claim of being an infrequent user, having taken only a few puffs at the last intake.

The urinary excretion half-lives of the later phases seemed to cluster around 4 days and from 6 days up to 10 days. The latter part of some curves indicated even longer half-lives. In a study by Lafolie et al. (9) a THCCOOH/C half-life of 32 days was observed. The present findings also agree with the mean plasma terminal elimination THCCOOH half-life of 4.3 days and an extreme of 12.6 days observed in heavy marijuana users by Johanson et al. (18). The corresponding extreme urinary excretion half-life was 9.8 days (7). These findings correspond with the fact that tetrahydrocannabinol (THC) distributes according to a multicompartment model with one very deep compartment, thought to be adipose tissue. A study has shown labeled Δ1-THC in fat biopsies four weeks after intake (19). However, body mass and weight seems to be only moderately predictive with regard to duration of cannabinoid-positive results as tested by EMIT (10).

The present results regarding urinary excretion profiles and detection times of cannabinoids (EMIT 20) and THCCOOH seem to be in accordance with those observed by others in frequent users (2,3) and frequent users (4,5,7,8). In both user groups, extensive periods of time were sometimes observed between the first cannabinoid-negative and the last cannabinoid-positive specimens. The duration of THCCOOH negative gaps up to six days in frequent users demonstrate that interpretation of urinary data should be done with great care.

The peak urinary THCCOOH concentrations were higher in the present study compared to the infrequent ones and so were the corresponding THCCOOH/C ratios. In one frequent user, a peak THCCOOH concentration seemed to appear about 40 h after intake. Huestis et al. (2) observed 28 h between THC intake and peak urinary THCCOOH concentration after a single smoked high dose in one out of six subjects, whereas the mean time to peak concentration after a high dose of marijuana was 13.9 h.

Regression analyses showed that correcting THCCOOH concentrations for creatinine improved the curve fit. The correlation coefficient was low in several of the subjects, especially in the late phases. Some could be ascribed to the increased imprecision of the assay near the detection limit of the method. Other, unknown factors could also be of importance. Applying first order kinetics to this phase might not be adequate. Applying first order kinetics to this phase might not be adequate. Applying first order kinetics to this phase might not be adequate. Applying first order kinetics to this phase might not be adequate. Applying first order kinetics to this phase might not be adequate.

In the early phase of urinary excretion (first two weeks), it was observed that the THCCOOH/C ratio could vary substantially. In later phases of excretion the THCCOOH/C ratio occasionally increased with a factor of 2.5 without suspicion of a new intake. However, one verified intake took place within the testing period, and a rather large increase in the THCCOOH/C ratio was observed. Similar increases were seen in others (A,G), clearly indicating new intakes. A new intake was not quite so obvious in subject I, and in subject F2, the increase in THCCOOH/C ratio was quite small. The present data demonstrate how difficult it is to discriminate between normal variation in urinary excretion and a limited new intake.

Correcting for creatinine could lead to a large extent account for the negative gaps that occurred in many of the subjects. Also, EMIT20 screening corrected for creatinine seemed to give a smoother curve. However, a confounding factor is the possibility of other cannabinoid metabolites contributing to the immunological screening result.

THCCOOH concentrations fluctuating around cutoff for extended periods became more frequent when the cutoff of the confirmation method was lowered. Decrease in THCCOOH cutoff concentration from 15.0 to 10.3 ng/mL increased the duration of THCCOOH positives substantially, and the EMIT20 cannabinoids were positive even longer. The discrepancy between the results from THCCOOH analyses and the immunological screening test (EMIT20) is well known and is due to other cannabinoid metabolites responding in the immunoassay. There were several negative screening results (7 out of 428) in the sense that EMIT20 negative samples contained THCCOOH above the cutoff (10.3 ng/mL). However, 22% of the EMIT20 positives were not confirmed using this cutoff. Lowering the cutoff of the THCCOOH confirmation method would have increased the number of confirmed positives and the time of THCCOOH detection. Raising the THCCOOH confirmation cutoff from 10.3 to 15.0 ng/mL would have decreased the number of confirmed positives in the present material. Thus, establishing cutoff is a balance between the need for detection of drug and the risk of spending resources by not being able to confirm the positive-screening results.

Conclusions

The urinary THCCOOH excretion profiles of frequent and infrequent cannabis users were followed for up to 38 days. The excretion half-life during the first five days after intake was
around 1.3 days in infrequent users, and a median half-life of 1.4 days was found in frequent users. In the latter group terminal excretion half-lives up to 10.3 days were observed. The ratio THCCOOH/C decreased the variability of the excretion curves as compared to THCCOOH concentration. However, considerable fluctuations in consecutive specimens were sometimes observed even after correction for creatinine. New cannabis intake was verified in one subject and was suspected in others. It was, in some instances, difficult to discriminate between fluctuations that were due to previous intake and new intake. Thus, making any firm conclusion regarding a new intake based on one or a few specimens may be difficult unless large increases in the THC-COOH concentration and the THCCOOH/C ratio are found or the time period between specimens is long.

Detection times of last THCCOOH- and cannabinoid-positive urine specimen and time to first negative specimen was increased in frequent users compared with infrequent users. The fluctuations around the cutoff were sometimes extensive.

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References


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