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# Time of drug elimination in chronic drug abusers Case study of 52 patients in a "low-step" detoxification ward

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**Abstract**

The elimination time of illicit drugs and their metabolites is of both clinical and forensic interest. In order to determine the elimination time for various drugs and their metabolites we recruited 52 volunteers in a protected, low-step detoxification program. Blood samples were taken from each volunteer for the first 7 days, daily, urine sample for the first 3 weeks, daily. Urine was analyzed using a fluorescence-polarization immunoassay (FPIA) and gas chromatography/mass spectrometry (GC/MS), serum using GC/MS. The elimination times of the drugs and/or their metabolites in urine and serum as well as the tolerance intervals/confidence intervals were determined. Due to the sometimes extremely high initial concentrations and low cut-off values, a few of the volunteers had markedly longer elimination times than those described in the literature. The cut-off values were as follows: barbiturates II (200 ng/ml), cannabinoids (20 ng/ml), cocaine metabolites (300 ng/ml), opiates (200 ng/ml). GC/MS detected the following maximum elimination times: total morphine in urine up to 270.3 h, total morphine and free morphine in serum up to 121.3 h, monoacetylmorphine in urine up to 34.5 h, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) in urine up to 433.5 h, THC-COOH in serum up to 74.3 h, total codeine in urine up to 123 h, free codeine in urine up to 97.5 h, total codeine in serum up to 29 h, free codeine in serum up to 6.3 h, total dihydrocodeine (DHC) in urine up to 314.8 h, free DHC in urine up to 273.3 h, total and free DHC in serum up to 50.1 h. Cocaine and its metabolites were largely undetectable in the present study. 

*Keywords:* Illicit drugs; Metabolites; Drug abusers; Drug elimination; Time dependency

## 1. Introduction

The pharmacokinetics and metabolism of illicit drugs are well-known for single and/or therapeutic doses [1–6], but the kinetics of long-term abuse of higher doses (cf. [8]) and of combinations of illicit drugs and their potential adverse effects are reported only from individual cases (review: [9]). Systematic studies are lacking as ethical and pragmatic considerations do not allow an investigation of drug addicts. However, recently a summary of empirical values was published by Schütz [10].

The objective of our study was to obtain data of the elimination time of illicit drugs during long-term substance abuse. These data may aid in outpatient or inpatient detoxification treatment and medico-legal problems such as issuing of driver licenses.

The preconditions of the drug dependence treatment unit (DDTU) of the Psychiatric Clinic North-Ochsenzoll in Hamburg, Germany, were decided to be adequate for such an investigation, because all patients volunteered for the

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detoxification treatment and gave their willing consent to participate in a prospective study. Moreover, illicit drug consumption during the study could be excluded by daily urine tests as well as — although retrospectively — by blood tests described here.

## 2. Materials and methods

### 2.1. Patients

Fifty-two users of illicit drugs who had volunteered for low-step, protected detoxification treatment in a psychiatric ward were enrolled in the study after meeting the following criteria:

1. informed consent;
2. adequate compliance;
3. veins suitable for taking blood samples.

The exclusion criteria were:

1. poor compliance;
2. severe accompanying organic and/or psychiatric disorders;
3. substitution with levomethadone or codeine before the study.

Forty-two of the patients were male (mean age 24.3 years), 10 were female (mean age 20.7 years). All of the patients were addicted to drugs, usually heroin ($n = 51$). All were treated according to the following therapeutic standard [11]: opiate detoxification with levomethadon (usual dosage: $2 \times 5$ mg) and, if needed, clonidine. Detoxification from benzodiazepines and barbiturates was done with clomethiazol or clonazepam.

### 2.2. Collections of samples

On each of the first 7 days after admission to clinic 10 ml of blood were taken from an arm vein. Urine samples were taken daily during the entire treatment period, which in most cases lasted 3 weeks. Urine and blood samples were frozen at $-20^{\circ}$C and subjected to chemical analysis several weeks later.

### 2.3. Chemical analysis

The urine samples were pretested using fluorescence-polarization immunoassays (FPIA) according to manufacturer's recommendations (ADx analyzer, Abbott GmbH, Diagnostika, D-65205 Wiesbaden, Germany). The following assays and cut-off values were used: barbiturates II (200 ng/ml), cannabinoids (20 ng/ml), cocaine metabolite (300 ng/ml), and opiates (200 ng/ml). The results of ''positive'' urine samples were confirmed by gas chromatography/mass spectrometry (GC/MS 5890/5971, Hewlett Packard Company, Palo Alto, CA, USA).

The serum samples were only analyzed by GC/MS. The preparation of urine and serum samples for GC/MS analyses includes a solid-phase extraction and derivatization with MSTFA. For the extraction CLEAN SCREEN® DAU and THC columns were used (United Chemical Technologies, Inc., Horsham, PA, USA). The extraction procedures were accomplished following the patterns of the column manufacturer. The quantitative GC/MS methods were done following established procedures [12,13] and calibrated using deuterated analogs of substances to detect. The detection limits (DL) are shown in Tables 1 and 2.

Table 1
Maximum concentrations of the drugs and their metabolites in urine at the time of first analysis[a,b]

| Drug | DL | Mean | S.D. | VC | Minimum | Maximum | Median | *n* |
|---|---|---|---|---|---|---|---|---|
| DHC | | | | | | | | |
| Total | 25 | 295650.9 | 292569.3 | 99.0 | 1716.0 | 1119740.0 | 206110.1 | 27 |
| Free | 10 | 97505.7 | 96895.6 | 99.4 | 364.0 | 437600.0 | 77940.0 | 27 |
| Codeine | | | | | | | | |
| Total | 25 | 12522.0 | 49188.3 | 392.8 | 59.0 | 344210.0 | 3056.5 | 48 |
| Free | 10 | 1466.9 | 3257.6 | 222.1 | 18.0 | 21950.0 | 554.5 | 46 |
| Morphine | | | | | | | | |
| Total | 25 | 117830.9 | 367414.4 | 311.8 | 280.0 | 2105929.0 | 20045.0 | 40 |
| Free | 10 | 4523.9 | 6242.1 | 138.0 | 100.0 | 24977.0 | 1891.0 | 39 |
| Monoacetylmorphine | 10 | 1180.9 | 1050.7 | 89.0 | 35.0 | 3699.0 | 968.5 | 21 |
| Cocaine | 50 | 497.6 | 628.1 | 126.2 | 61.0 | 1743.0 | 192.0 | 5 |
| Benzoylecgonine | 50 | 10992.4 | 17448.5 | 158.7 | 55.0 | 66449.0 | 5676.5 | 16 |
| Ecgoninmethylester | 50 | 2631.4 | 5857.8 | 222.6 | 110.0 | 23877.0 | 618.0 | 15 |
| THC-COOH | 10 | 260.4 | 456.4 | 175.3 | 14.0 | 2100.0 | 101.0 | 22 |

[a] GC/MS, data in ng/ml.
[b] DL = detection limit; S.D. = standard deviation; VC = variation coefficient.

Table 2
Maximum concentrations of the drugs and their metabolites in serum at the time of first analysis[a,b]

| Drug | DL | Mean | S.D. | VC | Minimum | Maximum | Median | *n* |
|---|---|---|---|---|---|---|---|---|
| DHC | | | | | | | | |
| Total | 25 | 2269.3 | 2694.4 | 118.7 | 34.0 | 11496.0 | 1494.0 | 25 |
| Free | 10 | 691.8 | 755.3 | 109.2 | 10.0 | 3214.0 | 443.0 | 25 |
| Codeine | | | | | | | | |
| Total | 25 | 155.0 | 414.9 | 267.7 | 25.0 | 1855.0 | 33.0 | 18 |
| Free | 10 | 33.3 | 55.8 | 167.7 | 10.0 | 200.0 | 12.0 | 10 |
| Morphine | | | | | | | | |
| Total | 25 | 226.8 | 234.3 | 103.3 | 29.0 | 1264.0 | 137.5 | 35 |
| Free | 10 | 23.3 | 14.3 | 61.3 | 11.0 | 68.0 | 17.0 | 15 |
| Benzoylecgonine | 25 | 86.5 | 62.7 | 72.5 | 27.0 | 207.0 | 55.5 | 6 |
| THC-COOH | 10 | 23.8 | 12.1 | 50.8 | 14.0 | 49.0 | 20.0 | 6 |

[a] GC/MS, data in ng/ml.
[b] DL = detection limit; S.D. = standard deviation; VC = variation coefficient.

### 2.4. Assessment

The maximum elimination time was defined as the interval between the start of control and the last time the cut-off values (ADx) or DLs (GC/MS) were exceeded. The tolerance intervals (confidence intervals) with which each drug is to be expected with 95% reliability within the detected interval were established [14].

In a second step the drug concentrations were measured and the median values and quartiles were calculated and graphed in 4 h intervals. The concentrations were presented logarithmically. The 95% confidence intervals were then calculated.

Table 3
Maximum elimination times (in hours) of the different drugs and their metabolites in urine[a]

| Drug | Mean | S.D. | VC | Minimum | Maximum | Median | *n* | Bratzke (1993) |
|---|---|---|---|---|---|---|---|---|
| Barbiturates | 100.6 | 88.2 | 87.7 | 1.0 | 264.5 | 62.4 | 10 | n.i. |
| Cannabinoides | 155.6 | 116.2 | 74.7 | 0.5 | 433.5 | 127.2 | 27 | 3 days per week |
| Cocain-metabolites | 38.8 | 34.4 | 88.6 | 0.2 | 118.0 | 29.1 | 16 | 3 days |
| Opiates | 87.0 | 46.1 | 53.0 | 0.5 | 273.3 | 72.8 | 51 | 3 days |

[a] ADx; S.D. = standard deviation; VC = variation coefficient.

Table 4
Maximum elimination times (in hours) of the different drugs and their metabolites in urine[a,b]

| Drug | Mean | S.D. | VC | Minimum | Maximum | Median | *n* |
|---|---|---|---|---|---|---|---|
| DHC | | | | | | | |
| Total | 128.7 | 69.0 | 53.6 | 48.3 | 314.8 | 120.8 | 27 |
| Free | 115.8 | 62.6 | 54.1 | 25.3 | 273.3 | 102.0 | 27 |
| Codeine | | | | | | | |
| Total | 25.6 | 22.9 | 89.3 | 0.3 | 123.0 | 24.5 | 48 |
| Free | 18.6 | 20.1 | 107.8 | 0.3 | 97.5 | 10.0 | 46 |
| Morphine | | | | | | | |
| Total | 118.8 | 45.7 | 38.5 | 25.3 | 270.3 | 121.6 | 40 |
| Free | 63.7 | 34.5 | 54.2 | 0.3 | 123.7 | 72.2 | 39 |
| Monoacetylmorphine | 5.0 | 7.2 | 144.2 | 0.5 | 34.5 | 3.0 | 21 |
| Cocaine | 6.8 | 9.1 | 134.1 | 0.5 | 24.8 | 2.5 | 5 |
| Benzoylecgonine | 47.4 | 32.6 | 68.8 | 0.3 | 118.0 | 49.0 | 16 |
| Ecgoninmethylester | 35.0 | 46.6 | 133.2 | 0.3 | 168.5 | 24.3 | 15 |
| THC-COOH | 117.5 | 118.0 | 100.4 | 0.1 | 433.5 | 74.3 | 22 |

[a] GC/MS, data in ng/ml.
[b] S.D. = standard deviation; VC = variation coefficient.

Table 5
Maximum elimination times (in hours) of the different drugs and their metabolites in serum[a,b]

| Drug | Mean | S.D. | VC | Minimum | Maximum | Median | *n* |
|---|---|---|---|---|---|---|---|
| DHC | | | | | | | |
| Total | 29.3 | 14.9 | 50.8 | 2.0 | 50.1 | 24.5 | 25 |
| Free | 24.7 | 13.1 | 52.9 | 2.0 | 50.1 | 24.5 | 25 |
| Codeine | | | | | | | |
| Total | 5.2 | 5.9 | 113.1 | 2.3 | 29.0 | 3.8 | 18 |
| Free | 4.0 | 1.1 | 26.8 | 2.7 | 6.3 | 4.3 | 10 |
| Morphine | | | | | | | |
| Total | 29.2 | 24.3 | 83.4 | 2.8 | 121.3 | 24.5 | 35 |
| Free | 14.4 | 29.5 | 205.6 | 2.0 | 121.3 | 4.0 | 15 |
| Benzoylecgonine | 5.1 | 1.6 | 31.7 | 2.5 | 7.2 | 5.4 | 6 |
| THC-COOH | 34.0 | 22.3 | 65.6 | 3.5 | 74.3 | 26.1 | 6 |

[a] GC/MS, data in ng/ml.
[b] S.D. = standard deviation; VC = variation coefficient.

Table 6
Correlation between the base-line concentrations of the different drugs and their maximum elimination times[a]

| Drugs | *n* | Initial concentrations (ng/ml) | | | Elimination time (h) | | | Correlation |
|---|---|---|---|---|---|---|---|---|
| | | Mean | Minimum | Maximum | Mean | Minimum | Maximum | |
| Total DHC (urine) | 25 | 295650.9 | 1716.0 | 1119740.0 | 128.7 | 48.3 | 314.8 | 0.491 |
| Total DHC (serum) | 27 | 2269.3 | 34.0 | 11496.0 | 29.3 | 2.0 | 50.1 | 0.604 |
| Total Codeine (serum) | 48 | 155.0 | 25.0 | 1855.0 | 5.2 | 2.3 | 29.0 | 0.970 |
| Total Codeine (urine) | 18 | 12522.0 | 59.0 | 344210.0 | 25.6 | 0.3 | 123.0 | 0.657 |
| Free morphine (serum) | 15 | 23.3 | 11.0 | 68.0 | 14.4 | 2.0 | 121.3 | 0.256 |
| Free morphine (urine) | 39 | 4523.9 | 100.0 | 24977.0 | 63.7 | 0.3 | 123.7 | 0.338 |
| Total morphine (serum) | 40 | 226.8 | 29.0 | 1264.0 | 29.2 | 2.8 | 121.3 | 0.173 |
| Total morphine (urine) | 35 | 117830.9 | 280.0 | 2105929.0 | 118.8 | 25.3 | 270.3 | 0.136 |
| Cocaine (urine) | 5 | 497.6 | 61.0 | 1743.0 | 6.8 | 0.5 | 24.8 | 0.964 |
| Benzoylecgonine (serum) | 6 | 86.5 | 27.0 | 207.0 | 5.1 | 2.5 | 7.2 | 0.269 |
| Benzoylecgonine (urine) | 16 | 10992.4 | 55.0 | 66449.0 | 47.4 | 0.3 | 118.0 | 0.433 |
| THC-COOH (urine) | 22 | 260.4 | 14.0 | 2100.0 | 117.5 | 0.1 | 433.5 | 0.449 |

[a] S.D. = standard deviation; VC = variation coefficient.

## 3. Results

The initial concentrations in urine and serum are summarized in Tables 1 and 2. The maximum elimination times including the distribution-free tolerance limits in urine are shown in Table 3 (ADx) and Table 4 (GC/MS), in serum in Table 5 (GC/MS). No consistently positive correlation was found between the amount of the initial concentration at the time of admission to the clinic and the maximum elimination time: the only positive correlation was for conjugated codeine in serum ($r > 0.96$) (cf. Table 6).

## 4. Discussion

The elimination time of illicit drugs and its metabolites depends on many variables, e.g. the dosage taken, the method of application, how long and how often the drug has been consumed, the types of drugs simultaneously consumed, and the body mass, age, sex and health status of the consumer (see also [10]). Moreover, determination of the maximum elimination time is clearly limited by the method of analysis, which affects cut-off and DLs.

Neither the dosage nor the length of the history of abuse are amenable to evaluation in drugs addicts. As a rule, the addicts themselves do not know, cannot remember, or provide this information. It is also all but impossible to know the catabolism promoting or hindering effect of simultaneously consumed drugs and their effects on drug concentrations in blood. Thus, the detection window after consumption of street drugs can only be based on empirical values.

The maximum elimination times obtained in the present study can be compared with the findings of other authors.

Statistical analyses have not yet been published on either the tolerance intervals or the maximum elimination times of drugs and their metabolites in chronic drug abusers. The maximum elimination times of drugs as detected by the ADx system are shown in Table 3. Our own observations agree largely with the data in the literature. In Table 3 our own findings are compared with those of Bratzke [15].

The present findings on the maximum elimination time of the heroin metabolite morphine in urine are different from those reported in the methodologically identical studies of Cone et al. [3,16] and Mitchell et al. [4]. However, the results of those authors were based on only four and six cases, respectively. Moreover, the methods of application (intramuscular/intranasal) and the dosage were dissimilar. This readily explains the distinct longer elimination times found in the present study.

The same applies, in principle, to the maximum elimination times in serum, in which the maximum observed elimination time in our own study was not only 24 h as reported by Skopp et al. [7], but for both morphine conjugates and free morphine, 120 h. However, the first study was based on intranasal application of 6 or 12 mg of heroin in only four cases.

As described in the literature in the present study the total codeine could be detected in urine for a similar length of time (123 h), whereas the maximum elimination time for codeine in the study of Cone et al. [17] was 108 h in four cases (intramuscular application). In the present study, however, codeine was apparently taken as an impurity of heroin. The initial concentrations in the present study were more than twice as high as those in the study of Cone and coworkers (344.210 versus 156.783 ng/ml).

The literature provides no data on the elimination time of dihydrocodeine (DHC) in urine and serum, so the present findings can be the basis for further investigations. The levels of DHC in serum given in the literature are similar to our own findings (cf. [18,19]), although Penning et al. [20,21] report concentrations twice as high.

Our findings of a maximum elimination time for cocaine in urine of 24 h as well as the levels of cocaine and its metabolites we detected in urine largely agree with the observation of other authors (cf. [22–25]). Because of the short half-life of cocaine in blood (detectable for ca. 6 h [15], or 8 h [9]), the maximum elimination time in serum was not determined. At most, its metabolites could be determined on the day of admission.

We could not detect THC in the serum of a single volunteer; according to the literature the detection time should be 5–12 h [26,27]. THC-COOH, by contrast, could be detected in serum for up to 74 h. This, however was considerably less than the heretofore described elimination time (albeit in a single case) of 25 days [28]. The highest THC-COOH levels in serum in the present study was 49 ng/ml, whereas Daldrup et al. [28] reported no comparable initial concentrations.

We detected the THC metabolite THC-COOH in urine up to 430 h (ca. 18 days), i.e. clearly longer than reported by Huestis et al. [5,6], but also shorter than found by other authors [9,15], who describe maximum elimination times in urine lasting not only several weeks, but several months. However, it must be pointed out that these extremely long elimination times were observed in only a few cases: up to 20 days [29] or longer — e.g. 90 days [28]. While it is true that the initial levels in our study in urine were approximately 10 times higher than those in Huestis et al. [6], they did not attain levels corresponding to those reported by the authors just mentioned.

Finally we must point out that even the elimination time reported here cannot by their very nature be considered to represent maximum values. The last consumption of illicit drugs outside the hospital remained unknown and, thus the real interval between drug application and the first determination of drug concentration in blood could not be considered in our analyses. Moreover, blood samples were taken only once daily, so that the final positive demonstration of the drug does not represent the maximum elimination time, which was reached at some point during the intervening 24 h period before the next-negative blood sample.

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