Very long Detection Times after High and repeated intake of Heroin and Methadone, measured in Oral Fluid

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ABSTRACT

When detection times for psychoactive drugs in oral fluid are reported, they are most often based on therapeutic doses administered in clinical studies. Repeated ingestions of high doses, as seen after drug abuse, are however likely to cause positive samples for extended time periods. Findings of drugs of abuse in oral fluid might lead to negative sanctions, and the knowledge of detection times of these drugs is important to ensure correct interpretation. The aim of this study was to investigate the detection times of opioids in oral fluid. 25 patients with a history of heavy drug abuse admitted to a detoxification ward were included. Oral fluid and urine were collected daily and, if the patient gave consent, a blood sample was drawn during the first five days after admission. Morphine, codeine and/or 6-monoacetylmorphine (6-MAM) were found in oral fluid and/or urine from 20 patients. The maximum detection times in oral fluid for codeine, morphine and 6-MAM were 1, 3 and 8 days, respectively. Positive oral fluid samples were interspersed with negative samples, mainly for concentrations around cut off. Elimination curves for methadone in oral fluid were found for two subjects, and the detection times were 5 and 8 days. Oral fluid is likely to become a good method for detection of drug abuse in the future.

Keywords:
Oral fluid, opioid, detection time, heroin, methadone

INTRODUCTION

Oral fluid is becoming increasingly popular as a specimen for the detection of drugs of abuse [1]. It is easy to collect, non-invasive and compared to urine or hair, a positive result in oral fluid can to a certain extent be interpreted as attributable to recent drug use. The detection window in oral fluid is considered to be more similar to blood, than urine [2]. In a previous study at our institute we have however shown that about 85 percent of the drugs of abuse detected in urine, were also detected in oral fluid collected simultaneously [3]. An overall agreement of 85% was likewise found between oral fluid and urine in a population of chronic pain patients [4]. The overlap between detection times in oral fluid and urine can be improved by using sensitive methods for oral fluid analysis [5].

The relationship between concentrations in oral fluid compared to blood has been studied in several publications [6,7], but variable ratios have been found. The transfer of drugs from blood to oral fluid depends on physicochemical factors as pH of the matrix, pka and lipid-solubility of the drug compound, and the fraction of drug molecules bound to proteins in plasma. Intercept® oral fluid device stimulates oral fluid production, and the drug compound, and the fraction of drug molecules bound to proteins have been found. The transfer of drugs from blood to oral fluid depends on several opiates leads to formation of these metabolites. Several studies have reported that 6-mam can be detected more frequently in oral fluid than in plasma. 25 patients with a history of heavy drug abuse admitted to a detoxification ward were included. Oral fluid and urine were collected daily and, if the patient gave consent, a blood sample was drawn during the first five days after admission. Morphine, codeine and/or 6-monoacetylmorphine (6-MAM) were found in oral fluid and/or urine from 20 patients. The maximum detection times in oral fluid for codeine, morphine and 6-MAM were 1, 3 and 8 days, respectively. Positive oral fluid samples were interspersed with negative samples, mainly for concentrations around cut off. Elimination curves for methadone in oral fluid were found for two subjects, and the detection times were 5 and 8 days. Oral fluid is likely to become a good method for detection of drug abuse in the future.

Pharmacokinetic studies have investigated the concentrations and detection times of heroin and metabolites in oral fluid after administration of low to moderate doses of heroin to healthy volunteers. After smoking 2.6–10.5 mg heroin base or taking 3–20 mg heroin HCl intravenously, 6-MAM was detectable for 0.5–8 and 1–4 hours, respectively [16]. Morphine was detected for 1–12 hours after smoking and for 1–4 hours after intravenous heroin administration. After intranasal administration of 12 mg heroin, 6-MAM and morphine were detectable for 4 and 8 hours, respectively [17]. Wang et al. administered 12 mg heroin intranasally to one subject, and 6-MAM was detected for 6 hours [18]. Codeine is reported to be detectable in oral fluid for 21 hours, after per oral ingestion of 60 or 120 mg [19].

Methadone is frequently prescribed as substitution treatment for opioid-dependence, but might also be diverted to the illegal market as a potent drug of abuse [20]. Methadone is reported to be detectable in oral fluid.
fluid from patients on maintenance treatment [21,22], and from pregnant women treated with methadone [10,15]. Our previous studies have shown very good correlation between findings of methadone in oral fluid and urine, collected simultaneously [3,23]. The detection time of methadone in oral fluid has however not been reported.

The pharmacokinetic studies of opioids in oral fluid from healthy volunteers after ingestion of low or moderate doses are not necessarily transferable to drug abusers, where the consumed doses are much higher, and repeated ingestions have taken place. For ethical and safety reasons, such high doses, of e.g. heroin or methadone, cannot be administered as part of a controlled pharmacokinetic study. This can however be studied in patients with a recent history of high ingestion of drugs of abuse, referred to a detoxification ward. The aim of this study was therefore to investigate the detection times of opioids in oral fluid from patients admitted to detoxification, during sustained, monitored abstinence.

MATERIALS AND METHODS

Participants

25 subjects undergoing drug detoxification for general drug abuse (opiates, amphetamines, benzodiazepines and cannabis in different combinations), were included in this study. The detoxification ward was a closed unit with medical and nursing personnel. Upon admission, all participant belongings were searched for drugs. Subjects had access to a secure courtyard area for recreation. All visitations were under constant supervision. A written consent was signed before start, and the study was approved by the Norwegian regional ethics committee.

The procedures followed were in accordance with the Helsinki Declaration of 1975. The analytical finding in this study did not have any consequences for the patients' treatment program. The analytical results were completed after the patients were released from the detoxification ward. Each patient was provided with a unique number. Only one person knew which names and numbers were connected, and this information was confidential for everyone else participating in the study.

The ingestions of drugs of abuse prior to admission were reported by the patients. Prescribed psychoactive drugs given during detoxification were reported by a physician.

Sample collection

The sampling period was 10 days after admission to the detoxification ward (day 0 to day 9). First void urine samples were collected every morning; however in a few cases, sampling was performed at a later time of the day, due to practical reasons. If the patient accepted, a whole blood sample was drawn during the first five days after admission to the detoxification unit. Oral fluid samples were collected every morning and evening. Oral fluid and urine samples were collected simultaneously in the morning, and for the first five mornings duplicate samples of oral fluid were collected.

Urine was collected in Vacutette® vials without additives (Med-Kjemi A/S, Asker, Norway). Whole blood was collected in 5 ml Vacutainer® tubes containing 20 mg sodium fluoride and 143 I.U. heparin (BD Vacutainer Systems, Belliver Industrial Estate, Plymouth, UK). The samples were stored at -20°C until analysis.

Oral fluid was collected using a commercially available collection device (Intercept® Oral Specimen Collection Device, OraSure Technologies, Bethlehem PA, USA). A cotton pad on a stick was placed in the mouth for two minutes. The collector pad contains sodium chloride, citric acid, sodium benzoate, potassium sorbate, gelatine, sodium hydroxide, and deionized water, and stimulates oral fluid production. The pad collects a mixture of saliva, gingival crevicular fluid and mucosal transudate, and after sampling it was placed into a vial containing 0.8 mL of stabilizing buffer solution and stored at -20°C until analysis. The preservative contains chlorhexidine digluconate, Flag Blue dye, Tween 20 (nonionic surfactant) and deionized water. The Intercept® device has been used in several other studies [24-26], and has been validated for detection of drugs of abuse [27].

Analyses

Urine samples were screened by immunological methods with a Hitachi 917 instrument for methadone and opiates using EMIT II Plus reagents from Siemens, SYVA and buprenorphine using CEDIA reagents from Termofisher, Microgenics. In addition pH and creatinine were measured. Positive opiate findings were confirmed with UPLC-MS-MS [28], while buprenorphine was confirmed by LC-MS/MS [29]. Methadone was confirmed with a modified version of the opiate method.

Whole blood was screened with UPLC-MS-MS [30] and positive opiate/opioid findings were confirmed with validated whole blood versions of the same method as for urine [28]. The sample preparation consisted of protein precipitation for the opiates [31], solid phase extraction with Waters Oasis MCX columns for methadone and liquid-liquid extraction with tertiary butyl methyl ether for buprenorphine.

Oral fluid samples were analysed by a quantitative UPLC-MS-MS method [32]. Chromatographic separation was achieved using an Aquity UPLC BEH C18 column (2.1x50 mm, 1.7µm). The mobile phase consisted of ammonium bicarbonate pH=8.5 (A) and methanol (B), with a gradient from 20% B to 90% B. Mass detection was performed by positive ion mode electrospray tandem mass spectrometry and included opiates, benzodiazepines, amphetamines, cannabis (THC) and cocaine.

Calculations

The findings in oral fluid were compared to the results from the urine samples, to be able to reveal if drugs were ingested during detoxification. A correction for creatinine levels were made for the drug concentrations in urine. The oral fluid samples were corrected for sample weight, and the reported concentrations are thus the concentrations of drugs in neat oral fluid.

Both duplicate samples of oral fluid were analysed, and the mean concentrations are reported. For a few samples, one of the results were below cut off and the other higher; for these samples the positive results were reported, since the aim of this study was to investigate for how long it is possible to get positive oral fluid findings after ingestion of drugs of abuse.

For patients who delivered blood samples, the drug concentrations were used to back calculate to estimate the drug dose that had been ingested.

Definition of detection time

The day of admission to the detoxification ward is named day 0 in this study, and the last day is day 9. This leads to a total of 10 days where
samples have been collected. Since drug ingestion might have taken place on day 0, only finding in the samples collected on day 1 have been considered as a detection time for 1 day. Naming the day the patients were admitted to the detoxification ward for day 0, makes it possible to read directly from the graphs, how many days' drugs have been detected after admission. This is thus the lowest estimate of detection time, since ingestion might have taken place some time before admission to the detoxification ward.

Since information regarding last drug ingestion is not known for certain, and is based on self reported information of drug use, a precise estimate of detection time in hours is not possible to provide from our data.

RESULTS

Table 1 shows demographic data from the 25 included patients, reported history of drug abuse and the drugs prescribed during the treatment period. Five females and 20 males were included in the study and the median age was 31 years (range 22-54). None of the participants were treated with heroin, morphine or codeine during detoxification. Three subjects were treated with methadone, 16 with buprenorphine and three with buprenorphine/naloxone. Nineteen patients participated for all ten days, eight for 6-9 days and eight for five days or less.

The cut-off values for the opioids in whole blood, urine and oral fluid are reported in table 2.

In Norway the cut-off levels are reported in micromole per litre, but since the majority of labs in other countries use gram units, this denomination is provided for the cut-off levels. The cut-off levels used in this study have been defined for our routine samples analysed at the institute in different forensic cases, and are equal to or higher than the analytical LOQ.

Opiates (morphine, codeine and 6-MAM)

Twenty of the included subjects had one or more opiates detected in oral fluid, urine or blood. Nineteen of the participants reported intake of heroin

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age</th>
<th>Days in Project</th>
<th>Opioid history before admission</th>
<th>Prescribed opioid during study period</th>
<th>Blood Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>34</td>
<td>10</td>
<td>Buprenorphine, heroin</td>
<td>Buprenorphine</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>29</td>
<td>1</td>
<td>Heroin</td>
<td>None</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>52</td>
<td>10</td>
<td>Heroin, SR-morphine</td>
<td>Buprenorphine</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>51</td>
<td>10</td>
<td>Heroin</td>
<td>Buprenorphine</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>31</td>
<td>5</td>
<td>Heroin smoking</td>
<td>None</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>22</td>
<td>9</td>
<td>Heroin inhaling</td>
<td>Buprenorphine</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>31</td>
<td>6</td>
<td>Heroin smoking</td>
<td>Buprenorphine</td>
<td>Y</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>29</td>
<td>7</td>
<td>Heroin, buprenorphine</td>
<td>Buprenorphine</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
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<td>10</td>
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<td>Buprenorphine, Heroin, methadone</td>
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</tr>
<tr>
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<td>Male</td>
<td>35</td>
<td>10</td>
<td>Heroin, methadone</td>
<td>Buprenorphine</td>
<td>Y</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>29</td>
<td>9</td>
<td>No opioids</td>
<td>None</td>
<td>Y</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>31</td>
<td>9</td>
<td>Heroin</td>
<td>Buprenorphine</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
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<td>44</td>
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<td>Buprenorphine</td>
<td>Y</td>
</tr>
<tr>
<td>14</td>
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<td>10</td>
<td>Heroin</td>
<td>Buprenorphine</td>
<td>Y</td>
</tr>
<tr>
<td>15</td>
<td>Female</td>
<td>37</td>
<td>1</td>
<td>Methadone</td>
<td>Methadone</td>
<td>N</td>
</tr>
<tr>
<td>16</td>
<td>Male</td>
<td>29</td>
<td>3</td>
<td>Heroin, SR-morphine</td>
<td>Buprenorphine and naloxone</td>
<td>Y</td>
</tr>
<tr>
<td>17</td>
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<td>43</td>
<td>10</td>
<td>Methadone, heroin</td>
<td>Buprenorphine</td>
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</tr>
<tr>
<td>18</td>
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<td>8</td>
<td>Heroin</td>
<td>Buprenorphine and naloxone</td>
<td>Y</td>
</tr>
<tr>
<td>19</td>
<td>Female</td>
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<td>8</td>
<td>Heroin, Buprenorphine</td>
<td>Buprenorphine and naloxone</td>
<td>Y</td>
</tr>
<tr>
<td>20</td>
<td>Male</td>
<td>54</td>
<td>6</td>
<td>Heroin, Methadone</td>
<td>Methadone</td>
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</tr>
<tr>
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<td>3</td>
<td>Heroin, SR-morphine</td>
<td>Buprenorphine</td>
<td>N</td>
</tr>
<tr>
<td>22</td>
<td>Male</td>
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<td>2</td>
<td>Heroin</td>
<td>Buprenorphine, Heroin, methadone</td>
<td>N</td>
</tr>
<tr>
<td>23</td>
<td>Male</td>
<td>52</td>
<td>2</td>
<td>Heroin, SR- morphine</td>
<td>Buprenorphine</td>
<td>N</td>
</tr>
<tr>
<td>24</td>
<td>Male</td>
<td>45</td>
<td>10</td>
<td>Heroin</td>
<td>Buprenorphine</td>
<td>Y</td>
</tr>
<tr>
<td>25</td>
<td>Male</td>
<td>34</td>
<td>10</td>
<td>No opioids</td>
<td>Methadone</td>
<td>Y</td>
</tr>
</tbody>
</table>

Y – yes (blood sample was collected) N – no (blood sample was not collected)
within the latest 24 hours prior to admission. For the last participant there was no information regarding last intake of heroin.

Figure 1 shows the elimination curves for morphine, 6-MAM and codeine in oral fluid and urine for five of the patients with long elimination times of heroin. Urine elimination curves for creatinine-normalized morphine are shown as inlet figures, to be able to compare the results from urine and oral fluid for each subject. The urine samples were not deconjugated before analyses of the opioids.

For the participants with positive findings of opiates in oral fluid, detection time ranged from 0-1 days for codeine, 0-3 days for morphine and 0-8 days for 6-MAM. In urine, the maximum detection times for codeine, morphine and 6-MAM were < 1, 1 and 4 days, respectively. Detection times are also reported for the subjects who left the detoxification ward before finishing the 10 days study period, and some of the patients did not have negative samples before leaving.

For two of the participants (patient 16 and 22), not shown in figure 1, the maximum morphine concentrations in oral fluid were around 1100 ng/ml (4 µM), detected in the first sample taken on the admission day, and the corresponding 6-MAM concentrations were around 290 ng/ml (1 µM). The morphine concentrations were 10-100 times higher than the maximum morphine concentrations found in samples from the other participants. Both patients with these very high morphine concentrations participated in the study for less than two days, and the detection time could thus not be recorded.

The mean 6-MAM/morphine ratio in oral fluid was 0.28 and varied from 0.02-1.1. Only one sample had a 6-MAM/morphine ratio > 1. This specimen was collected on day 0.

Whole blood samples were drawn from 14 of the 25 subjects. Morphine was detected in blood from two of these subjects in low concentrations (11ng/ml / 0.04 µM for patient 13 and 20 ng/ml / 0.07 µM for patient 16), whereas codeine and 6-MAM were not detected in any of the blood samples.

**Methadone**

The excretion profiles in oral fluid and urine are shown in figure 2 for the two participants where methadone excretion could be investigated. Only patient 10 participated in the study to study day 9, and the last sample was negative. Patient 7 participated to study day 5, and the last sample was still positive.

Patient 7 participated to study day 5, and the last sample was still positive. The detection times in oral fluid were longer compared to the urine findings using our standard urine cut-offs. Detection of the methadone metabolite EDDP in urine did not lead to longer detection time of methadone. For all the samples that screened positive with an immune assay, both methadone and EDDP were positive. A specific analysis for all urine samples would however have been likely to give a longer detection time based on EDDP findings.

Methadone was only detected in whole blood from one of the patients (concentration of 710 ng/ml / 2.3 µM for patient 25), and this patient was treated with methadone during the study period.

**Other opioids**

Buprenorphine alone, or in combination with naloxone, were prescribed to 18 patients during detoxification, including all patients with a previous history of buprenorphine use. No elimination curves for buprenorphine were therefore available from this study.

The oral fluid samples were, in addition to heroin metabolites, buprenorphine and methadone, screened for fentanyl and oxycodone, but no positive samples were found.

**DISCUSSION**

For ethical and safety reasons, high doses of heroin or methadone cannot be administered as part of a controlled pharmacokinetic study. Such drug use can however be studied in patients with a recent history of high ingestion of heroin and methadone, referred to a detoxification ward, during sustained, monitored abstinence. We found maximum detection times in oral fluid for codeine, morphine and 6-MAM of 1, 3 and 8 days. This is much longer than reported from previous studies, where low doses have led to maximum detected time of 8 and 12 hours for 6-MAM and morphine, respectively (16,17). Our study shows that 6-MAM was detected for 5 days, or more, in 4 subjects. The corresponding urine samples taken from these subjects, showed decreasing morphine concentrations, and did not indicate any new intake of heroin.

It has been suggested that detection of 6-MAM, but not morphine, in oral fluid, is consistent with very recent heroin use, either by smoking or

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**Table 2.** Cut off levels for analysis in whole blood, oral fluid and urine. The cut off levels are the level used in our routine analyses for the different matrixes, and are equal to, or higher than LOQ.

<table>
<thead>
<tr>
<th></th>
<th>Whole blood (ng/mL)</th>
<th>Oral fluid (ng/mL)</th>
<th>Urine quantification (ng/mL)</th>
<th>Urine screening (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MAM</td>
<td>9.8</td>
<td>1.6</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>Buprenorphine/</td>
<td>0.9</td>
<td>2.3</td>
<td>193</td>
<td>5</td>
</tr>
<tr>
<td>Buprenorphine gluc*</td>
<td>9.0</td>
<td>3.0</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td>Codeine</td>
<td>62</td>
<td>16</td>
<td>62</td>
<td>300</td>
</tr>
<tr>
<td>Methadone</td>
<td>NA</td>
<td>NA</td>
<td>111</td>
<td>NA</td>
</tr>
<tr>
<td>EDDP</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>300</td>
</tr>
<tr>
<td>Morphine</td>
<td>8.6</td>
<td>5.7</td>
<td>29</td>
<td>NA</td>
</tr>
<tr>
<td>Opiates</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>300</td>
</tr>
</tbody>
</table>

NA Not analyzed

* Buprenorphine is measured as buprenorphine glucuronide in urine

Cut off levels in oral fluid is reported in oral fluid without buffer (corrected with a factor of 3 compared to measured values)
**Figure 1.** Concentration–time profiles for morphine, codeine and 6-MAM in oral fluid (ng/mL), and the creatinine corrected morphine concentrations in urine as inlet figure (ng/L per mg/L) for five patients admitted to detoxification.
The present study demonstrates that detection of 6-MAM might be the only finding in oral fluid several days after cessation of high and repeated intake of heroin, but in the samples collected the first days after admission, the concentrations of morphine, by far, exceed the corresponding concentrations of 6-MAM. A controlled study, where different doses of heroin were administered, suggested that a ratio of 6-MAM/morphine >1 in oral fluid is consistent with heroin use within the last hour before specimen collection. In our study the ratio of 6-MAM/morphine was >1 in only one specimen from patient number 21, and this was the first specimen taken after admission. There was however no information regarding last intake of heroin in this subject. In the rest of the specimens the ratios of 6-MAM/morphine were less than 1. This supports the findings from the study conducted by Presley et al., since we started the collection several hours after cessation of drugs of abuse in our study, and the pharmacokinetic during the initial phase was not followed.

For three of the patients, morphine-negative specimens were interspersed with morphine-positive specimens. The time between two positive specimens ranged from 1-3 days. The number of days with negative 6-MAM specimens before a positive specimen ranged from 1-7 days. The longest time with negative specimens before a positive specimen was observed in subject four. The first specimen post-admission (day 0) was positive for morphine and codeine. The rest of the specimens were negative, with respect to morphine, codeine and 6-MAM, except for the specimen taken on study day eight, which was positive for 6-MAM. The urine samples taken during the study period, including the specimen collected in the morning on day 8, were all negative for opiates, speaking against a new intake.

An important implication from the present study is that a positive specimen for either 6-MAM or morphine following a negative specimen not necessarily be attributed to a new intake of heroin. From our findings, this seems to be relevant mainly for low 6-MAM concentrations, around cut off. Subject 19, did however show a substantial increase in the concentrations of both morphine and 6-MAM on day 3, despite decreasing concentrations of morphine in the urine samples. There was no suspicion of new ingestion.

For two of the participants, very high morphine concentrations were measured in oral fluid, from 10-100 times higher than the maximum morphine concentrations from the other participants. A blood sample was taken from subject 16, and back calculation of the concentration to the start of detoxification, revealed that the morphine concentration had been around 570 ng/ml (2 µM) at day 0. The patient reported that he had ingested 500 mg sustained-release morphine two days before admission at the detoxification ward, and 500 mg heroin intravenously the same day.

Codeine was only detected in oral fluid or urine samples collected at day 0. Kim et al. have reported that ingestion of 120 mg codeine as a single dose can be detectable in oral fluid for 72 hours. In our study the detected of codeine is likely to be due to ingestion of acetyl codeine, found as a contamination of illicit heroin. The codeine concentrations are thus much lower, compared to ingestion of codeine as a parent drug, and a shorter detection time is as expected.

Methadone was detected in all the oral fluid and urine samples from the patients treated with methadone, and the concentrations were much higher compared to concentrations in samples from patients where methadone was not prescribed. Elimination curves of methadone were...
only found for two patients, and revealed detection time in oral fluid ranging from 5-8 days.

Subject 10 reported that last intake of 150 mg methadone was on the day before admission, and methadone was not administered during the study period. Methadone was only detected in urine for 5 days; the detection time for EDDP in this case was not longer.

Using the cut-off levels selected in this study, we found longer detection time for methadone in oral fluid compared to urine. Methadone is basic in nature, and the lower pH in oral fluid (pH 6.2-7.4) compared to serum, leads to higher concentrations of basic drugs in oral fluid [9,35]. From our data the concentrations of methadone decrease steadily with time during the initial elimination phase, comparable to what is found in urine. In the later phase of elimination, when methadone is no longer found in urine, negative specimens could be interspersed between positive specimens. Such findings will depend on the selected cut-off levels for the different matrices.

In our study we have used the cut-off levels defined for our routine samples analysed at the institute in different forensic cases.

A weakness of our study is that the information regarding last ingestion of drug, and the amount ingested, prior to admission, is based on self-report. Since blood samples were only possible to take from some of the participating patients, and many of these were collected several days after admission, the self-reported information could not be verified by concentrations of these drugs in blood at day 0. Detection time is calculated from admission at the hospital at day 0, and this is likely an underestimate.

Negative specimens interspersed between positive specimens were found for low drug concentrations, around cut off. Even though a correction of oral fluid volume in performed in these samples, no correction of the oral fluid concentrations can be made, as for creatinine in urine. Without such a correction factor, a larger variation is likely to be seen for the concentration curves. It is thus as expected that concentrations around cut-off will vary between positive and negative results, and are also reported in other studies [36]. This phenomenon is also known from urine samples [37].

It is challenging to make drug dependent patients participant in studies with collection of both oral fluid and urine samples for 10 days. Nine patients did however participate for all ten days, eight for 6-9 days and eight for five days or less, although, not all the planned samples were collected.

During detoxification, the intention was to avoid treatment with psychoactive drugs

Patients admitted to this treatment, have however been using high doses of psychoactive drugs for a very long time, and cessation will lead to major abstinence. Most of the patients were thus treated with daily doses of methadone or buprenorphine and decreasing doses of oxazepam, nitrazepam, zolpidem or zopiclone. Since the prescribed drugs are registered, elimination could be studied for other drugs of abuse, ingested prior to treatment.

CONCLUSION

This study shows the elimination of heroin and methadone in oral fluid compared to urine, collected from drug abusers admitted to a detoxification ward after repeated ingestion of high doses of drugs of abuse for several years. The results revealed much longer detection times for opioids in oral fluid than previously reported; as long as 8 days for heroin and methadone. Negative samples interspersed with positive determination were encountered for morphine, 6-MAM and methadone, mainly for concentrations around cut off.

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