Comparison of the Various Opiate Alkaloid Contaminants and Their Metabolites Found in Illicit Heroin with 6-Monoacetyl Morphine as Indicators of Heroin Ingestion

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Abstract

In this study the use of the various opiate alkaloid contaminants as potential markers for illicit heroin ingestion were investigated. Urine samples (n = 227) taken from prisoners for routine drug screen, which were positive for opiates by immunoassay screening, were analyzed for contaminants in illicit heroin. A previously described method was used for the analysis; urines were extracted using mixed-mode solid-phase extraction; the extracts were derivatized using N-methyl-bistrifluoroacetamide and N-methyi-N-trimethylsilyltrifluoroactamide/trimethylchlorosilane. The derivatized extracts were subjected to electron impact gas chromatography-mass spectrometry. The extracts were injected in full scan mode followed by selected ion monitoring mode for target opiate alkaloids found as contaminants in illicit heroin. The opiate alkaloids and their metabolites specifically targeted included meconine, desmethylmeconine, hydrocotarnine, acetylcodeine, codeine, morphine, 6-monacetylmorphine (6-mare), papaverine, hydroxypapaverine, and dihydroxypapaverine. Of the 227 samples positive for opiates by immunoassay, using a cut-off of 300 ng/mL, 199 were confirmed positive for morphine and using a cut-off of 10 ng/mL, 28 were confirmed positive for 6-mam. Using the screening method described in the study, the following numbers of positives were found: 199 for morphine, 103 for codeine, 5 for meconine, 46 for desmethylmeconine, 18 for 6-mam, 136 for hydroxypapaverine, and 139 for dihydroxypapaverine. Acetylcodeine, hydrocotarnine, and papaverine were not detected in any of the samples. The results of this study show that analysis for papaverine metabolites is more sensitive than 6-mare as a way of demonstrating illicit heroin use.

Introduction

Heroin or diacetylmorphine is metabolized to 6-monoacetyl-morphine (6-mam), which is then further metabolized to morphine. If morphine is detected in urine, 6-mam must be detected in order to prove that it is the result of heroin ingestion. 6-Mam is only detectable in urine for 2-8 h compared with morphine, which is detectable for 1-2 days (1). Because of this difference in detection window, it is often not possible to demonstrate that morphine detected in the urine is because of heroin ingestion.

Screening urine for drugs of abuse is routinely performed on the prison population of England and Wales. During this screening, morphine is sometimes detected and it is possible that the morphine could be due to the ingestion of illicit heroin, but unless 6-mam is found, it cannot be proven.

Codeine containing preparations can be available for use as analgesics in the prison population, and as codeine is metabolized to morphine, the morphine could be due to the ingestion of codeine. Illicit heroin contains small amounts of acetylcodine, which is metabolized to codeine. After ingestion of illicit heroin, the amount of morphine detected in urine is always much greater than the amount of codeine. After ingestion of codeine, the relative proportion of codeine and morphine varies between individuals and as a function of time (2). Morphine is eliminated more slowly than codeine, and depending on the cut-offs used for the assays, it is possible to detect morphine only after codeine ingestion (2). Therefore, the ratio of codeine to morphine can suggest whether codeine or illicit morphine has been ingested, but when morphine is present in small amounts usually no codeine is detected.

In addition to morphine, street heroin contains various alkaloids extracted from the opium poppy, Papaver somniferum, including codeine, thebaine, noscapine, and papaverine (3). During the production of heroin, morphine is acetylated to diacetylmorphine. Codeine, which is also present in the extract, is acetylated to form acetylcodine. Therefore, detection of acetylcodine in urine proves ingestion of illicit heroin (4), but the study by O'Neal and Poklis in 1997 (5) concluded that acetylcodine was found in fewer specimens and at lower concentrations than 6-mam, and their study in 1998 (6) concluded that acetylcodine was not a reliable biomarker of illicit heroin use because of the low concentrations present in urine. Acetyl-
codeine has a similar half-life to 6-mam; neither remains detectable in urine for as long as morphine following heroin use (7,8). McLachlan-Troup et al. (9) investigated the potential to distinguish between the use of street heroin and pharmaceutical diamorphine through the detection in urine of various opiate alkaloids originating in the opium poppy. They concluded that detection in the urine of the metabolites of noscapine and metabolites of papaverine were useful for this purpose (9). Detection of these metabolites in urine also has the potential to show that morphine detected in urine has been derived through the use of street heroin rather than codeine.

The aims of the study were to investigate whether any of the various opiate alkaloids or their metabolites originating from the opium poppy, present as contaminants of illicit heroin, could be used to show if morphine in the urine of prisoners was because of consumption of illicit heroin and to determine if any of the opiate alkaloids or their metabolites were better indicators of heroin use than 6-mam.

Materials and Methods

The samples used for this study were taken as part of the routine screening carried out by the Prison Service. All samples were anonymized, and there were no consequences for the prisoners as a result of this study.

Materials

All solvents were analytical grade and were purchased from VWR (Poole, U.K.). Methyleneoxamphetamine-d₃ (MDA-d₃) was obtained from Promochem (Welwyn Garden City, U.K.). Bakerbond Narc-2 mixed-phase cartridges were from Trichema (Warrington, U.K.). Derivatizing reagent N-methyl-bis trifluoroacetamide (MSTFA) + 1% trimethylchlorosilane (TMCS) was from Perbio (Cramlington, U.K.). 4-Hydroxyxypapaverine (97.8%), 3-hydroxyxypapaverine (97.9%), and 3,4-dihydroxyxypapaverine hydrobromide (96.9%) were custom synthesized by Edinburgh Pharmaceuticals (Edinburgh, U.K.). Ammonium hydroxide, chemicals, and all other drug standards were purchased from Sigma-Aldrich (Poole, U.K.). The DB-5 capillary column was from Crawford Scientific (Strathaven, Scotland). Drugs of abuse controls were obtained from DPC (Llanberis, U.K.).

Samples

Two hundred and twenty seven urine samples of those submitted for routine screening for drugs of abuse and found positive for opiates at 300 ng/mL using the Cedia® immunoassay technique had the opiates (morphine, 6-mam, codeine, and dihydrocodeine) confirmed as normal by gas chromatography-mass spectrometry (GC–MS) in the laboratory carrying out this work on behalf of the Prison Service. The remaining sample was then forwarded to the Toxicology Unit at Imperial College London for analysis for the various opiate alkaloids and their metabolites. The staff of the Toxicology Unit was blinded to the confirmation results. Among the samples submitted to the Toxicology Unit were two control samples, and the Toxicology Unit was also blinded to this.

Method of analysis

The urines were analyzed by mixed-mode solid-phase extraction (SPE) followed by GC–MS using a previously described procedure (10). In summary, after addition of internal standard (1.5 mL, 0.67 mg/L MDA-d₃ in 1M acetate buffer pH 5), urines (4 mL) were incubated overnight with β-glucuronidase (Helix pomatia, 50 µL) at 60°C. After cooling, the sample was adjusted to pH 8 and then subjected to SPE using Bakerbond narc-2 columns. These are mixed-mode columns and allowed the simultaneous extraction of acidic, basic, and neutral compounds. After conditioning the columns with methanol (2 mL), followed by distilled water (2 mL), followed by 0.1M phosphate buffer pH 6 (2 mL), the sample was applied. After the column had been washed with distilled water (2 mL), 0.01M acetic acid (250 µL) was applied. Chloroform/isopropanol (80:20) (2 × 1.5 mL) was then used to extract the acidic/neutral drugs followed by chloroform/isopropanol/ammonium hydroxide (80:20:3) (2 × 1.5 mL) to extract the basic drugs. The extracts were combined. MBTFA (25 µL) was added, and they were dried down under nitrogen at 90°C. The extracts were further derivatized with MSTFA/TCMS (50 µL) followed by MBTFA (25 µL). An aliquot of the sample (1.0 µL) was injected onto the GC–MS.

Instrumentation

A Hewlett-Packard (HP) 6890 series GC fitted with a split-splitless injector with an HP7683 automatic liquid sampler interfaced with an HP5973 mass selective detector were...
used (Agilent, Stockport, U.K.). The analytical column was a DB-5 (crosslinked 5% phenyl methyl siloxane, 30 m x 0.25-mm i.d., 0.25-μm film thickness) fitted with a retention gap (uncoated, deactivated silica) (1 m x 0.25-mm i.d.). Temperature conditions were as follows: initial temperature of 80°C for 2 min, increased to 310°C at 16°C/min, held for 5 min, giving a total run time of 21 min. The flow of the carrier gas (helium) was maintained at 1.0 mL/min in constant flow mode. The injector port was set at 280°C. The GC–MS was programmed to perform a 1.0-μL splitless injection. The samples were analyzed using full scan (55–550 amu). The samples were then re-injected and analyzed using a selected ion monitoring (SIM) program to monitor the target opiate alkaloids listed in Table I.

Control material
A control was run with each batch of samples to check retention times and performance of the assay. The control material was diluted with blank urine to give the following concentrations in mg/L: amphetamine-d, 1.25; benzoylecgonine, 0.375; codeine, 0.75; methadone, 0.25; metamfetamine-d, 1.25; morphine, 0.075; morphine-3-glucuronide, 1.325; oxazepam, 0.25; secobarbital, 0.5; and tetrahydrocannabinolic acid, 0.0625.

Data acquisition
The software used for data acquisition was HP Enhanced Chemstation G1701BA version B.01.00. In addition to the 61 drugs routinely looked for in the drug treatment patients, various opiate alkaloids were specifically targeted. An additional macro was written in-house for this software, which performed target compound analysis for the specific opiate alkaloids. The following opioids were available as pure standards and were put through the analytical procedure producing the following derivatives: codeine, hydroxyacpapaverine, and 6-mam formed TMS derivatives; morphine and dihydroxyacpapaverine, the 2TMS derivatives; papaverine and acetylcodeine did not derivatise; thebaine was not detected; and noscapine broke down to give meconine and hydrocotarnine. Pure standards for meconine and hydrocotarnine were not available, but as these compounds did not derivatise, they were matched with spectra in a standard reference library (11). Pure standard desmethylnoscapine was not available, so this compound was identified by matching the retention time and spectra obtained from the elucidation of this urine metabolite as reported previously by McLachlan-Troup et al. (9). Desmethylnoscapine had previously been synthesized on a micro scale to allow confirmation of the structure of this urine metabolite. Neither desmethylnoscapine, hydroxypapaverine, nor dihydroxyacpapaverine were available in sufficient quantities to allow for any quantitation. The GC retention time, target ions, qualifier ions, and ion ratios used for the target opiate alkaloids are shown in Table I. The limit of detection using scan was taken as a signal equal to or greater than 10 times the baseline noise; the limit of detection using SIM was taken as a signal equal to or greater than three times the baseline noise. Using scan the limit of detection was 50 ng/mL for morphine and 200 ng/mL for 6-mam, and using SIM the limit of detection was 20 ng/mL for morphine and 25 ng/mL for 6-mam. To identify a positive, the retention time had to be within 1% of the standard for those compounds where a standard was available. For a full scan spectrum match there had to be at least an 80% match with the ions in the standard spectrum. Using SIM three ions were used, and the ratio of these ions had to be within 10% of the ratio for these ions in the standard spectrum. The opiate alkaloids were first matched using the scan trace. If the signal to noise was less than 10 then the SIM trace was used.

Results and Discussion

Figure 1 shows the main metabolic pathways for papavrine and noscapine. Papavrine is metabolized by being demethylated to form four different hydroxylated metabolites and a dihydroxy metabolite (12), though noscapine is metabolized by a C-C bond cleavage to meconine, which is then demethylated to form desmethylnoscapine (13). Figure 2 shows typical extracted ion chromatograms, and Figure 3 shows the ion spectra for desmethylnoscapine-TMS, hydroxyacpapaverine-TMS, and dihydroxyacpapaverine-2TMS. A standard for desmethylnoscapine was not available; however, McLachlan-Troup et al. had synthesized

![Figure 1](https://academic.oup.com/jat/article-abstract/30/4/267/709441/269)
this metabolite on a micro-scale to confirm the structure of the postulated TMS derivative (9). The hydroxypapaverine window shows four peaks, each peak has the ion spectra for hydroxypapaverine-TMS, suggesting the four peaks correspond to TMS derivatives of the four different species of hydroxy metabolites; when four peaks are seen, the peak height ratios vary, though peak 1 is invariably the largest. The dihydroxypapaverine window shows two peaks, both peaks have the ion spectra of dihydroxypapaverine-2TMS; two peaks are always seen, but the peak height ratio of the two peaks varies slightly. It has been postulated that there is one dihydroxy metabolite of papaverine (12), but our findings suggest that there are two major dihydroxy-papaverine metabolites corresponding to the characteristic two peaks shown on GC–MS.

Table II shows the number of samples positive for the target opiate alkaloids. Of the 227 samples received, 199 were positive for morphine. Acetylcodine, hydrocotarnine, and papaverine were not detected in any of the samples. Acetylcodine has a retention time very close to morphine (retention times of 15.85 and 15.75 for acetylcodine and morphine, respectively) and has common ions. The ions used for monitoring morphine (429, 414, and 236) are not present in acetylcodine, but the ions used for monitoring acetylcodine (341, 282, and 229) are present in morphine. The GC–MS conditions were not modified to allow for better separation of morphine and acetylcodine, as previous studies had shown that acetylcodine was not suitable for confirmation of street heroin ingestion (5,6).

Noscapine broke down during the analytical procedure to form meconine and hydrocotarnine; noscapine is also metabolized to meconine. Meconine was detected in five urine samples, but hydrocotarnine was not detected at all. This indicates that the meconine detected was the metabolic product of noscapine rather than the analytical breakdown product and that the amount of unchanged noscapine excreted was too low to be detected. The amount of unchanged papaverine was probably also too low to be detected. It is known that less than 1% of a dose is excreted unchanged (12).

Compound analgesics containing codeine are used in the prison population, and 103 samples were positive for codeine. There were two samples positive for codeine but negative for morphine and a further 32 samples where the peak area was greater for codeine than morphine. No contaminants of street heroin or papaverine/noscapine metabolites were detected in any of these 34 samples. In these 34 cases the codeine is most probably due to ingestion of codeine rather than illicit heroin. In the remaining 69 samples the codeine could have been due to metabolism of acetylcodine, which is present in all samples of illicit heroin, although it is possible that there could have been ingestion of both codeine and illicit heroin.

One hundred and thirty six samples were positive for hydroxypapaverine, and 139 were positive for dihydroxypapaverine, and all samples, which were positive for hydroxypapaverine, were also positive for dihydroxypapaverine; only 3 samples were positive for dihydroxypapaverine alone. As the amounts of the papaverine metabolites present were very small, we concluded that a sample should only be reported positive if both hydroxy and dihydroxypapaverine were present. For both metabolites, a positive was determined by first checking the scan spectra; if the retention time matched, the spectra matched using the stated criteria, and the signal-to-noise ratio was greater than 10, then a positive was reported; if the signal-to-noise was less than 10, then SIM was used. Again, if the retention time and the target ion ratios matched and the signal to noise was greater than 3, then a positive was reported. One hundred and thirty six of the 199 (68%) samples positive for morphine were positive for papaverine metabolites.

Of the samples testing positive for morphine, 18 were positive for 6-mam and 136 were positive for papaverine metabolites. All samples, which tested positive for 6-mam, were also positive for papaverine metabolites. The SPE GC–MS method described here had a cut-off for 6-mam of 200 ng/mL using scan or 25 ng/mL using SIM. This method is used in scan for routine screening of drug treatment patients. This allows the detection of unknown as well as targeted drugs. In drug treatment patients, finding morphine alone is considered indicative of heroin ingestion.

**Figure 2.** Typical extracted ion chromatograms of desmethylmeconine-TMS (100:100:60) (A), hydroxypapaverine-TMS (100:90:25) showing the characteristic 4-peak pattern (B), and dihydroxypapaverine-2TMS (100:75:30) showing the characteristic 2-peak pattern (C).
Five samples were positive for meconine, and all of the samples that were positive for meconine were positive for desmethylmeconine. Forty six of the 199 (23%) of the samples positive for morphine were positive for desmethylmeconine. All samples which were positive for meconine were positive for hydroxy and dihydroxy-papaverine. Only 1 sample, which was positive for desmethylmeconine, was not positive for hydroxy-papaverine/dihydroxy-papaverine. This shows that using this methodology, papaverine metabolites are better indicators of illicit heroin ingestion than noscapine metabolites.

The laboratory carrying out routine drug testing for the Prison Service use criteria broadly based on the U.K. Workplace Drug Testing Forum criteria with cut off levels specific to HM Prison Service for England and Wales, which are 300 ng/mL for the immunoassay screening for opiates; 300 ng/mL for morphine, codeine, or dihydrocodeine confirmation; and 10 ng/mL for 6-mam confirmation. Using these criteria, the laboratory found the same number of samples positive for morphine, but 28 samples positive for 6-mam compared with 18 positive for 6-mam when using a cut-off of 25 ng/mL.

The alkaloids thebaine, papaverine, and noscapine are present in poppy seeds (14). Consumption of poppy seeds gives rise to the presence of morphine and codeine in urine (15-18). Cassella et al. (19) proposed thebaine as a direct marker for poppy seed use although the work of Meadway et al. (17) found that the elimination of thebaine varied widely between individuals, suggesting that its absence from a specimen was not necessarily indicative of opiate abuse. The presence of noscapine or papaverine and their metabolites were not included in any of these studies. Four volunteers (staff at the Toxicology Unit) ate a lunch of poppy seed rolls and cake. The urine from these volunteers was collected at 2, 4, and 24 h and analyzed using the same method as for the analysis of prisoner’s urine. Morphine was shown to be present, but not papaverine metabolites (unpublished data). As both the country of origin and the preparation of the seeds can influence the concentration of the various alkaloids (20), a more comprehensive study is proposed using poppy seeds from different origins. Although papaverine is found in poppy seeds, there is a need to establish whether or not consumption of papaverine-containing poppy seeds can produce metabolites in sufficient quantities to be detectable in urine.

This study shows that the number of samples where ingestion of street heroin was indicated increased by a factor of five using detection of papaverine metabolites rather than 6-mam. There are two published papers concerning the pharmacokinetics of papaverine (21,22); Belpaire et al. (21) concluded that excretion of papaverine metabolites was essentially complete within 24 h, and Wilen et al. (22) concluded that 80% of a given dose of papaverine was excreted within 48 h. These are relatively old studies using old technologies. Recent studies with the National Addiction Centre, Institute of Psychiatry, Kings College London suggest that papaverine has a similar window of detection as morphine (23). Further studies are proposed to establish a more precise estimate of the detection window for papaverine metabolites in urine.

Papaverine is a smooth muscle relaxant and vasodilator. It is not licensed for use in the U.K. but is available in other countries including the USA, although it is only available on prescription. Papaverine is also an ingredient papaveretum, which is a preparation containing predominantly morphine but contains other opiate alkaloids, the formula varying from...
was included in the questionnaire completed by each volunteer.

Therefore, although the presence of papaverine metabolites found in urine of street heroin users are due to the intake of prescribed papaverine medication, although it is always a possibility.

Brenneisen and Hasler studied the pyrolysis products from diacetylmorphine and adulterants of street heroin samples (24). They found that papaverine was heat stable but noscapine was pyrolyzed to a greater extent. In the study with the National Addiction Centre, the route of administration of the street heroin was included in the questionnaire completed by each volunteer. Using this information, it was shown that papaverine metabolites were detected in the urine of subjects who injected or smoked the street heroin (19).

The method is in routine use for analyzing samples from drug treatment patients. Immunoassay screening is not used as these samples are nearly all positive and positive for a number of drugs. Routinely, scan only is used. This has the required sensitivity for routine clinical work, including the detection of papaverine metabolites, and the advantage of scan is that unknowns can be detected. However, using scan the limit of detection for 6-mam is 200 ng/mL. This is acceptable for routine clinical work (unlike work place drug testing) as detecting morphine is interpreted as indicating heroin/diamorphine ingestion. For this study, SIM was used in order to increase the sensitivity for 6-mam to 20 ng/mL. One of the clinics served by the Toxicology Unit is treating clients with injectable diamorphine. As 6-mam is a metabolite common to both diamorphine and illicit heroin it cannot be used to distinguish between the two substances. In order to find out if these clients are using illicit heroin, in addition to the prescribed diamorphine, the compounds routinely looked for using scan include desmethymecopine, hydroxypapaverine, and dihydroxypapaverine.

The quantities of contaminants in illicit heroin vary depending on the country of origin of the opium poppy and the method of production of the heroin. It is possible that some batches of illicit heroin may contain little or no papaverine. Therefore, although the presence of papaverine metabolites can show ingestion of street heroin, it does not follow that the absence of papaverine metabolites shows that illicit heroin has not been used. Papaverine metabolites cannot be a definitive marker for illicit heroin use, but this study does show papaverine metabolites are a more useful indicator of heroin use than 6-mam. The samples screened in this study came from various prisons throughout England and Wales, suggesting the heroin had been derived from a variety of sources.

### Table II. Number of Samples Positive for Target Opiate Alkaloids

<table>
<thead>
<tr>
<th>Drug</th>
<th>No positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphone-2TMS</td>
<td>199</td>
</tr>
<tr>
<td>6-Mam-TMS</td>
<td>18</td>
</tr>
<tr>
<td>Codeine</td>
<td>103</td>
</tr>
<tr>
<td>Meconine</td>
<td>5</td>
</tr>
<tr>
<td>Desmethylcodeine-TMS</td>
<td>46</td>
</tr>
<tr>
<td>Hydroxypapaverine-TMS</td>
<td>136</td>
</tr>
<tr>
<td>Dihydroxypapaverine-2TMS</td>
<td>139</td>
</tr>
<tr>
<td>Acetylmorphine</td>
<td>0</td>
</tr>
<tr>
<td>Hydrocotamine</td>
<td>0</td>
</tr>
<tr>
<td>Papaverine</td>
<td>0</td>
</tr>
</tbody>
</table>

country to country. Papaveretum is used to supplement anaesthesia in particular pre-operative medication, and it is combined with salicylate to form a compound analgesic. It is unlikely that papaverine metabolites found in urine of street heroin are due to the intake of prescribed papaverine medication, although it is always a possibility.

Brenneisen and Hasler studied the pyrolysis products from diacetylmorphine and adulterants of street heroin samples (24). They found that papaverine was heat stable but noscapine was pyrolyzed to a greater extent. In the study with the National Addiction Centre, the route of administration of the street heroin was included in the questionnaire completed by each volunteer. Using this information, it was shown that papaverine metabolites were detected in the urine of subjects who injected or smoked the street heroin (19).

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### Conclusion

During routine screening of urine samples using standard procedures and cut-offs, 6-mam was detected in 28 out of a batch of 199 morphine positive samples, showing that the morphine was due to heroin ingestion in 14% of the samples. Using the method described in this paper, papaverine metabolites were detected in 136 out of 199 morphine-positive samples, showing that the morphine was due to heroin ingestion in 68% of the samples. This shows that papaverine metabolites were five times more effective as an indicator of heroin ingestion than 6-mam. Further studies, preferably quantitative, are needed before detection of papaverine metabolites can be used routinely to confirm ingestion of illicit heroin. These studies include the need to establish the time window for the detection of papaverine metabolites in urine after heroin ingestion and to establish if the ingestion of poppy seeds containing papaverine can give rise to significant concentrations of the papaverine metabolites in urine. The data presented here shows that papaverine metabolites are better than noscapine metabolites as indicators of illicit heroin use.

### Acknowledgments

The authors would like to thank The Drug Strategy Unit of HM Prison Service for funding this study and for allowing the data to be submitted for publication. The authors would also like to thank Medscreen for providing the samples and the data from the routine screening of samples for HM Prison Service.

### References


