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# Analysis of Narcotics in Urine: A Review

Kriti Nigam[1]*, AK Gupta and Amit Chattree

Department of Forensic Science, SHIATS, Allahabad, Uttar Pradesh, India.

## Review Article

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***For Correspondence**

Department of Forensic Science,
SHIATS, Allahabad, Uttar Pradesh, India.

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**ABSTRACT**

Analysis of narcotic drugs in body fluids are the choice of research since last two decades. The methods of analysis has been widely enhanced in the past few years. The analysis of narcotic drugs in urine sample is preferred among other body fluids as drugs and its metabolites found in urine are usually stable and are present in higher concentration as compared to other biological fluids. These are also detectable for a relatively longer period of time. Several techniques for the qualitative as well as quantitative analysis of narcotic drugs are reviewed in this paper ranging from conventional chromatographic methods to the modern UPLC-MS/MS and Micellar Electrokinetic Capillary Chromatographic methods, in order to suggest a better, efficient, fast and result oriented method that can be utilized in future work of analysis.

## INTRODUCTION

The term 'narcotics' originally refers to "any psychoactive compound with sleep inducing properties". This also shows a developmental character such as mood elater or enhancer of physical efficiency. Most of such compounds are used under medical prescription and supervision with a dose control. Familiarity with them is the modern problem with enhanced doses as per requirement. Such chemicals have special property of dependence with a compulsion. Economically the difficulties in availability of such compounds promote the monitory benefits to the seller and permanent damage to the user. List of such dangerous formulations is increasing every day. So there is an urgent requirement to develop such advanced techniques of identification which can cope up with the need. Urine is the preferred biological specimen for the analysis of such drugs as drugs and drug metabolites found in urine are usually stable are present in higher concentrations in urine than in other biological materials and are detectable for relatively long period of time. Some great efforts have been made in this field:-

**Debrabandere et al** determined buprenorphine and its major metabolites, N-desalkyl buprenorphine in urine samples by using reversed phase HPLC with electrochemical detection. Results were compared with those obtained from a commercial RIA test. This test is only capable of detecting buprenorphine concentration higher than 1ng/ml [1].

**O'Neal and Poklis** report a sensitive opiate gas chromatographic-mass spectrometric assay that detects AC, diacetylmorphine, and the propionylated derivatives of codeine, morphine, 6-MAM, and norcodeine. The analytes were extracted by solid phase with recoveries from 62 to 98%. Thus, suggested acetylcodein (AC) in addition to 6-monoacetylmorphine (6-MAM), as a marker for the use of illicit heroin [2].

**Cassella et al** determined that consumption of poppy seeds in various foods may lead to a positive opiate result in urine subjected to testing for drugs of abuse. As a natural constituent of poppy seeds, thebaine was investigated as a possible marker for poppy seed consumption. Poppy seeds were examined for opiate content by gas chromatography-ion trap mass spectrometry (GC-MS) after extraction with methanol. Urine samples spiked with thebaine and urine from subjects given 11 g of poppy seeds were tested for the presence of thebaine, codeine, and morphine. Street heroin, one morphine and one codeine tablet, and urine from individuals who had used heroin were also examined for thebaine. Urine specimens were screened by enzyme immunoassay (EMIT) and confirmed for thebaine

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by GC-MS using a solid-phase extraction method. Thebaine was detectable in the urine of poppy seed eaters in concentrations ranging from 2 to 81 ng/mL. Because thebaine was absent in powdered drugs and the urine of true opiate drug users, thebaine is proposed as a direct marker for poppy seed use [3].

**O'Neal et al** reported a sensitive opiate gas chromatographic-mass spectrometric assay that detects acetylcodein (AC), diacetylmorphine, and the propionylated derivatives of codeine, morphine, 6-MAM, and norcodine. The analytes were extracted by solid phase with recoveries from 62-98%. Thus, suggested AC in addition to 6-monoacetylmorphine (6-MAM), as a marker for the use of illicit heroin [4].

**O'Neal et al** have investigated Acetylcodeine (AC), an impurity of illicit heroin synthesis, as a urinary biomarker for detection of illicit heroin use. One hundred criminal justice urine specimens that had been confirmed positive by GC/MS for morphine at concentrations > 5000 ng/ml were analyzed for AC, 6-acetylmorphine (6AM), codeine, norcodeine and morphine. The GC/MS analysis was performed by solid phase extraction and derivatization with propionic anhydride. Total codeine and morphine concentrations were determined by acid hydrolysis and liquid/liquid extraction. AC was detected in 37 samples at concentrations ranging from 2 to 290 ng/ml (median, 11 ng/ml). 6AM was also present in these samples at concentrations ranging from 49 to 12 600 ng/ml (median, 740 ng/ml). It was concluded that due to its very low concentration in urine, AC was much less reliable biomarker for illicit heroin use than 6-AM in workplace or criminal justice urine screening programs [4].

**Krenn et al** developed a new reverse phase (RP) HPLC method for the separation of the main opium alkaloids morphine, codeine, thebain, papaverin and noscapine on a non-porous (micropellicular) stationary phase. The analysis time for the opium alkaloid was approximately 1/10 of that on porous stationary phase [5].

**Baden et al** have evaluated cross-reactivity of quinolone antimicrobials in common opiate screening assays and to assess the in vivo implications of this phenomenon. It was found that nine of the quinolones caused assay results above the threshold for a positive result in at least 1 of the assays. Four of the assay systems caused false-positive results for at least 1 quinolone. Eleven of the 13 compounds caused some opiate activity by at least 1 assay system. At least 1 compound caused opiate assay activity in all 5 assay systems. Levofloxacin, oflaxacin, and perfloxacin were most likely to lead to a false-positive opiate result. Positive results were obtained in urine from all 6 volunteers [6].

**Staub et al** developed the procedures for quantification of (a) morphine, 6-monoacetylmorphine (6-AM), and codeine in urine and (b) diacetylmorphine and AC in urine. Solid-phase extraction of the analytes was performed, and the extracted analytes were analyzed by selected-ion monitoring with gas chromatography-mass spectrometry. This procedure required prior derivatization with propionic anhydride. Different validation parameters were determined, such as linearity, reproducibility, extraction recoveries, and cutoffs. Seventy-one urine specimens of illicit heroin abusers and 44 urine specimens of subjects in a heroin maintenance program were analyzed. AC was detected in 85.9% of the samples of the first group but not in any of the samples from subjects taking medical heroin [7].

**Bogusz et al** have found the following substances as markers of non-prescription heroin: acetyl codeine (AC); its metabolites codeine (C) and codeine 6-glucuronide (C6G); papaverine (P); and noscapine (N). Typical heroin markers diamorphine (DAM) and its metabolites monoacetylmorphine (MAM) and morphine (M) were also determined. The drugs were extracted from urine samples with solid-phase extraction (C18) using standard 200-mg columns and 96-well microplates (100 mg). The extracts were examined with liquid chromatography-atmospheric pressure chemical ionization mass spectrometry (positive ionization) in two isocratic systems. Selected ion monitoring procedures were applied for protonated molecular masses and characteristic fragments of drugs involved. The limits of detection were in the range of 0.5-1 ng/mL urine. The occurrence of selected heroin markers was investigated in 25 urine samples collected from heroin abusers (road traffic offenders and overdosed patients). C6G was found in all samples, C in 24 samples, N in 22 samples, MAM in 16 samples, P in 14 samples, DAM in 12 samples and AC in 4 samples. The appearance of these compounds in urine reflects their pharmacokinetic properties and the composition of non-prescription heroin [8].

**Brenneisen et al** checked the feasibility of an analytical monitoring of concomitant consumption of street heroin. Profiling of 170 street heroin samples has shown that >95% contained 1-5% of 6-acetylcodeine (AC). After solid-phase extraction of 10 ml-urine aliquots, resulting in a recovery of 84-92% AC, GC/MS in the SIM mode was used for quantitation. The identification of AC was based on the target ion m/z 341 and the ion ratios of the other characteristic ions m/z 282 and 229. The ions m/z 341 (AC) and 344 (AC-$d_3$, internal standard) were evaluated to quantitate AC. The limit of quantitation was 0.22 ng/mL, whereas the intra- and inter-day precision (n = 6, 10 ng/mL level) of the method was 3.2 and 7.4%, respectively. Thus, demonstrated the reliability of the AC urine monitoring as a potential tool for the detection of use of street heroin [9].

**Rohrig and Moore** showed that positive results caused by poppy seed ingestion can be differentiated from those caused by heroin or morphine abuse, the screening cutoff concentration for urine opiates was raised to 2000 ng/mL from 300 ng/mL by this study [10].

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**Musshoff et al** have described a fully validated procedure for the simultaneous determination of morphine (MOR), morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G), 6-acetylmorphine (6AM), codeine (COD), codeine-6-glucuronide (C6G), acetylcodeine (AC), noscapine (NOS) and papaverine (PAP) based on liquid chromatography followed by electrospray mass spectrometry applying multiple reaction monitoring (LC-ESI-MS/MS) in urine samples. The extraction was carried out on a Zymark Rapid Trace Workstation using C18 solid-phase extraction cartridges. The separation was performed in 19 min on an Agilent 1100 HPLC system, using a Phenomenex C18 AQUA column (4 micron, 150 mm x 2 mm), which is coupled with an Applied Biosystems API 2000 mass spectrometer. Deuterated analogues were used as internal standards. The limits of detection were in the range of 0.1 ng/ml (PAP) to 7.4 ng/ml (M6G), the coefficients of correlation were higher than 0.996, the precisions ranged from 3% to 12% and the absolute recoveries were between 45% (M3G) and 98% (MOR). It was concluded that after the ingestion of pharmaceutical heroin only general markers for heroin use were detected, which are MOR, M3G, M6G and 6AM, respectively. When illicit heroin was abused, additionally to further general markers (COD, C6G) specific markers for non-prescription heroin abuse (AC, NOS, PAP) were found [11].

**Yang et al** developed a new competitive inhibition immunoassay (group-selective immunoassay; GSI) to detect free morphine in urine with the Fab' fragments of monoclonal antibodies (MAbs) (1B(12)F(9)B(4), IgG(1), kappa, K(aff) = 9.66 x 10(10)M(-1)). At the first assay step, micro titer plates were coated with morphine-ovalbumin (M-6-S-OVA), in which free amino acids were protected by a glutaraldehyde cross-linking modification. At the second assay step, anti-morphine MAbs' Fab' fragments, in which free amino groups were biotinylated by N-hydrosuccinimide-biotin ester, were bound to chemically modified immunosorbent. The biotin residues were then detected by the streptavidin-peroxide conjugate. This method has a sensitivity of 3.50 x 10(-15) mol/L using very little volume of sample, covering up to almost 1.20 x 10(-11) mol/L of standard concentration of morphine with good reproducibility. Standard curve prepared in urine indicated a good correlation between the concentration of morphine and the value of OD (y = 1/ax + b; r = 0.99939257, S = 0.01138127). The recoveries were 94 approximately 101.4% from negative urine and 95.2 approximately 107.5% from positive urine samples, respectively [12].

**Trawkowski et al** determined various compounds that appear in urine after consumption of poppy seeds. These compounds are considered to be the putative markers of heroin (HER) abuse whereas acetylcodein is found as a marker of illicit preparation ("Street HER"). It was concluded in the study that besides acetylcodein (problem of short half life), only noscapine and papaverine, but not their metabolites, might be cautiously used as additional markers of illicit HER abuse as they have not been detected after oral intake of poppy seeds in normal doses [13].

**Musshoff et al** have mentioned that in case of cannabinoids, serial monitoring of THC-COOH to creatinine ratio can differentiate between recent drug use and residual THC-COOH excretion in urine. For the assessment of the extent of the cannabis use, the determination of the free and bound THC-COOH and especially of THC and 11-OH-THC glucuronides is found to be useful but need further confirmation [14].

**Alnajjar et al** developed a new capillary electrophoresis method for the screening of human urine for multiple drug of abuse. The electrolyte composition was modified by using beta-cyclodextrin and organic solvents. A sequential injection solid phase extraction (SI-SPE) system was also constructed. The combination of SI-SPE and sample stacking showed significant sensitivity enhancement with limits of detection in the range 5-30ng/ml. Overall, this automated and miniaturized SI-SPE system provide a rapid, sensitive and robust procedure for analysis, as well as minimize sample and solvent consumption [15].

**Kauppila et al** detected the opiates, cannabinoids, benzodiazepines and amphetamines from urine samples obtained from drug users by using Desorption and Electro Spray Ionization (DESI-MS) and the results were compared to the results obtained from GC-MS experiments. It was found that analytes could be detected by DESI-MS measurements even after a hundred fold dilution indicating the sensitivity of DESI, which could further be increased by optimizing the spray solvent composition [16].

**Babiker et al** have suggested the detection and characterization of thebaine as a urinary marker of opium use, as it is a major constituent of opium. Thebaine is found to form a trimethylsilyl (TMS) derivative. Upon GC-MS analysis, thebaine was detected as doublet peak in total ion chromatograms (TICs) by both quadruple and ion-trap without derivatization [17].

**Ghumatkar et al** developed an immunoassay technique for the rapid analysis of metabolites and drugs of abuse from urine. However, GC-MS should be used to confirm the immunoassay results [18].

**Lin et al** have established a cation-selective exhaustive injection and sweeping micellar EKC to analyze morphine and its four metabolites, including codeine, normorphine, morphine-3-glucuronide and morphine-6-glucuronide. Five addict's urine specimens were analyzed. The results showed good co-incidence with LC-MS/MS [19].

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**Sun et al** have tried to establish a liquid chromatography – tandem mass spectrometry method for the simultaneous analysis of cocaine and its metabolites benzoylecgonine in urine samples and found the method highly sensitive and specific and suitable for the simultaneous analysis of cocaine and benzoylecgonine in urine samples [20].

**Musshoff et al** suggested the comparison of urine results concerning co-consumption of illicit heroin and other drugs in heroin and methadone maintenance program and found the chromatographic routine procedure for the determination of heroin marker substances in urine sample very useful [21].

**Heim and Pugh** investigated the potential use and practical application of comprehensive multi-dimensional gas chromatography- time of flight-mass spectrometry (GCXGC-TOF-MS) in forensic toxicology analysis for a diverse range of illicit drugs in urine sample without derivatization. A total of 11 drugs of abuse and metabolites were detected in analysis of non-derivatized drugs spiked in urine [22].

**Langman et al** developed an LC-MS/MS method for detection and quantitation of cocaine, benzoylecgonine, norcocaine, cocaethylene, m-hydroxybenzoylecgonine, anhydroecgonine ethyl ester and anhydroecgonine methyl ester in urine. Two hundred samples previously analyzed by gas chromatography (GC) coupled with MS were extracted using solid-phase extraction. Chromatographic separation was achieved using a gradient consisting of mobile phase A [20 mM ammonium formate (pH 2.7)] and mobile phase B (methanol/acetonitrile, 50:50), an XDB-C(8) (50 x 2.1 mm, 1.8 micro m) column and a flow rate of 270 micro L/min. Concentrations were calculated by comparing the peak-area with the internal standard. The results of GC-MS and LC-MS/MS measurements of cocaine and benzoylecgonine showed good correlation [23].

**Jong et al** determined heroin metabolites including morphine, codeine and 6-acetyl morphine by cation-selective exhaustive injection and sweeping micellar electrokinetic chromatography. Liquid- liquid extraction was used for urine pre-treatment. An uncoated fused silica capillary was filled with phosphate buffer containing 30% methanol, then high conductivity buffer was followed. Samples were injected electro kinetically. The sweeping and separation were performed at -25kv using phosphate buffer and 80mM sodium dodecyl sulfate. The baseline separation was done within 10 min. The RSD and RE values in intra-day and inter-day assays were all below 20%, which showed good precision and accuracy. Their detection limits were 10ng/ml [24].

**Lombardo et al** described the simultaneous determination of four drugs, two local anesthetics and two opium alkaloids (noscapine and papaverine) by capillary zone electrophoresis with solid phase extraction using Oasis HLB cartridges. Their recoveries ranged from 81 to 107% at the target concentrations of 2.0, 5.0 and 8.0 microgmL (-1) in spiked urine samples. The assay is very specific for these compounds and requires a short sample preparation procedure prior to the electrophoretic analysis [25].

**Shakleya et al** quantified Opiates, cocaine, and their metabolites by liquid chromatography-mass spectrometry (LC-MS) in 284 urine specimens, collected thrice weekly, to monitor possible drug relapse in 15 pregnant heroin-dependent women. Opiates were detected in 149 urine specimens (52%) with limits of quantification (LOQ) of 10-50 micro g/L. Morphine, morphine-3-glucuronide, and/or morphine-6-glucuronide were positive in 121 specimens; 6-acetylmorphine, a biomarker of heroin ingestion, was quantifiable in only 7. No heroin, 6-acetylcodeine, papaverine, or noscapine were detected. One hundred and sixty-five urine specimens (58%) from all 15 participants were positive for one or more cocaine analytes (LOQ 10-100 micro g/L). Ecgonine methylester (EME) and/or benzoylecgonine were the major cocaine biomarkers in 142. Anhydroecgonine methylester, a biomarker of smoked cocaine, was positive in six; cocaethylene and/or ecgonine ethylester, biomarkers of cocaine and ethanol co-ingestion, were found in 25 [26].

**Kriger et al** described a novel method for the analysis of cocaine, benzoylecgonine, and cocaethylene by using ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS). Sample preparation has been minimized to a simple deproteinization step in which each specimen is mixed with an acetonitrile-internal standard mixture. The method has excellent precision across the linear range of 25-2,000 ng/mL for each analyte. With a run-time of 4 min, this method provides a significant improvement over traditional GC/MS methods [27].

**Nieddu et al** determined four thiophenethylamine designer drugs (2C-T series) simultaneously in human urine are reported. The quantitative analysis was performed by capillary electrophoresis with mass spectrometric detection (CE/MS), using 2,5-dimethoxy-4-methylthiophenethylamine-D(4) (2C-T-D(4)) as internal standard. The method was specific, sensitive, and reliable for the analysis of these derivatives in urine samples [28].

**Hidvegi et al** tried to identify Cannabigerol (CBG), which in its acid form is one of the main intermediates in the biosynthesis of cannabinoids in hemp, in urine specimens of confirmed cannabis users. It is shown that enzymatic hydrolysis is necessary for the formation of free neutral cannabinoids from conjugates. After extraction, derivatization with N-Methyl-N-(Trimethylsilyl) tri fluoro acetamide (MSTFA) and GC/MS analysis, peaks of characteristic fragment ions (m/z 337, 391, 377 and 460) of bis-trimethylsilyl derivative of CBG appeared at 12.48 minutes in both real sample and the urine spiked with CBG. It was shown that CBG enters the body and it is extracted in urine in the conjugated form, similar to other neutral cannabinoids. The presence of CBG metabolites, such as its

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glucuronated form, was examined by analyzing the chromatograms of hydrolyzed and tri methylsilylated extracts. A compound in the Cannabis consumers' urine extracts was detected, having fragment ions at m/z 425, 465 and 479 at the retention time of 14.19 min which is presumed to be the 4"-hydroxy-CBG or 5"-hydroxy-CBG[29].

**Shang et al** made a new approach for fast and sensitive U V detection of 12 kinds of narcotic drugs on a microfluidic device by micellar electrokinetic capillary chromatography. Under optimal sampling and separation conditions, the base line separation of 12 drugs with resolution values ranging from 1.06 to 4.04 and separation efficiency up to $5.14X10^5$ plates/m was achieved within 200s. This system is highly useful in the analysis of narcotic drugs in human urine with the aid of liquid- liquid extraction of the sample [30].

**Verplaetse and Tytgat** developed a highly sensitive Liquid - Chromatography tandem Mass Spectrometry method for simultaneous analysis of nine narcotic analgesics and metabolites in urine and whole blood. Sample preparation was performed on a mixed -mode cation exchange solid phase extraction cartridge with an additional alkaline wash step. Mobile phase of high pH was used. Gradient elution with 10mM ammonium bicarbonate (pH 9.0) and methanol was performed on a small particle column. All the parameters were successfully evaluated and method showed high sensitivity for the analysis of several forensic cases involving narcotic analgesics [31].

## CONCLUSION

Analysis of narcotics is important not just for an investigation in which a foul play is suspected it is equally essential for determining accidental deaths and suicides and even for substance abuse.

Many noteworthy analytical techniques have been reported by the toxicologist based on the several chromatographic and spectroscopic methods. The techniques involve analysis of narcotic from urine for both qualitative as well as quantitative interest, which not only have high resolution values but also greater separation efficiency. Almost all the techniques are highly sensitive and require minimal sample requirement in addition of easy sample preparation.

Micellar Electrokinetic Capillary Chromatography and Liquid Chromatography tandem Mass Spectrometry are the recent emerging trends in the simultaneous analysis of these drugs in urine.

Besides all the techniques reported so far there is a need to develop other economical techniques with the better sensitivity and finest resolution in order to provide speedy determination of narcotic drugs in urine.

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