

Drugs of Abuse—Opiates and Related Drugs

TESTING FOR CODEINE, MORPHINE, HYDROCODONE, HYDROMORPHONE, DIHYDROCODEINE, OXYCODONE, OXYMORPHONE, AND 6-ACETYLMORPHINE IN URINE, SERUM, AND PLASMA

Clinical Background

- Patient compliance with opiate and related pain medications (opioids) can be effectively monitored by periodic urine drug testing.
- Urine is the preferred specimen; serum or plasma may be utilized for patients who are unable to provide a urine specimen (e.g., dialysis patients) or to support pharmacokinetic evaluations.
- Testing for identification and quantification of other opioids used commonly to manage pain (e.g., methadone, propoxyphene, fentanyl, buprenorphine) is available separately.

Methodology

- ARUP utilizes state-of-the-art liquid chromatography-tandem mass spectrometry (LC-MS/MS) to detect and quantify opioids.
- The reporting limit (limit of quantitation) is 5 ng/mL for urine and 2 ng/mL for serum and plasma.
- The glucuronide conjugates are not hydrolyzed during sample preparation to allow detection of 6-acetylmorphine along with seven prescription opioids. Therefore, those drugs that form glucuronide conjugates (all but hydrocodone) are reported as "free" to indicate that only the unconjugated form has been identified and quantitated.

Indications for Ordering

- Testing is designed to identify and quantitate classical opiates and related drugs that interact with opioid receptors (opioids). Testing is designed to support pain-management clinics, rehabilitation services, and other health care providers with patients who are exposed chronically to opiates and related drugs. Urine is the specimen of choice. Results may be useful to detect:
 - Compliance with prescribed opioids
 - Use of non-prescribed opioids
- Serum and plasma may be used to evaluate drug pharmacokinetics.

- Related drug analyses are available for urine, serum, and plasma:
 - Methadone and EDDP (methadone metabolite)
 - Propoxyphene and norpropoxyphene (propoxyphene metabolite)
 - Fentanyl and norfentanyl (fentanyl metabolite)
 - Buprenorphine and metabolite
 - Multi-drug panels (up to nine drug classes) may be ordered with reflexed confirmatory testing based on a positive initial test (immunoassay)

Limitations

- Time periods of drug detection vary with specimen type and drug. Urine is the most commonly used specimen due to convenience of collection and because drug use can be detected for the longest period with urine.
- Results of this testing cannot identify the formulation of drug used, the dose administered, or the specific time(s) of drug administration.
- Dilution of urine specimens through over-hydration (excessive intake of fluids prior to voiding) may compromise detection limits.

Interpretation

- Possible explanations for drug(s) prescribed, but not detected:
 - Non-compliance
 - Dilute urine, leading to drug concentrations that fall below analytical detection limits
 - Accelerated metabolism due to drug-drug interactions, altered expression of drug-metabolizing enzymes, or genetic variation
 - Poor drug absorption
- Possible explanations for drug(s) detected, but not prescribed:
 - Drug metabolism (see discussion below)
 - Lack of disclosure of other prescriptions from health care providers
 - Voluntary use of non-prescribed drug(s)
 - Incorrect prescription filled

- Possible explanations for unexpected drug concentrations:
 - Dosing less or more frequently than prescribed
 - Time-lapse between last dose and specimen collection
 - Other variables as described above
- Many opioids are both prescription drugs and metabolites of other opioids (see figure 1). Differentiating between production from metabolism and direct use of an additional drug is sometimes difficult. If the patient does not have a prescription for the drug(s) and/or metabolite(s) identified, other explanations should be considered. Two general categories of metabolism are major pathways and minor pathways. The percentage ratios provided were derived from an ARUP database review in 2006 that included 2,114 positive urine opioid test results.
- Major pathways:
 - Morphine from codeine
 - When the free morphine concentration, as a percent of free codeine in a urine specimen, is less than 55 percent, the presence of morphine may be the result of metabolism.
 - The conversion of codeine to morphine is mediated by the cytochrome P450 isozyme 2D6 (CYP2D6), an enzyme that is known to exhibit genetic variability. Genetic testing for *CYP2D6* variants is available separately.
 - Morphine and 6-acetylmorphine from heroin
 - Detection of 6-acetylmorphine, along with morphine, is definitive evidence for the use of heroin. However, failure to detect 6-acetylmorphine (short half-life) with morphine present does not rule out use of heroin.
 - Morphine can be derived from other sources such as poppy seeds, codeine, and morphine-containing medications.
 - Hydromorphone and/or dihydrocodeine from hydrocodone
 - When the free hydromorphone concentration, as a percent of hydrocodone in a urine specimen, is less than 30 percent, the presence of hydromorphone may be the result of metabolism.
 - The percentage of dihydrocodeine derived from metabolism of hydrocodone is not well characterized.
 - Oxymorphone from oxycodone
 - The percentage of oxymorphone derived from metabolism of oxycodone is not well characterized.
- Minor pathways:
 - Hydrocodone from codeine
 - Oyler, et al.1 report that hydrocodone may derive from metabolism of codeine.
 - When the hydrocodone concentration, as a percent of free codeine in a urine specimen, is less than 40 percent, the presence of hydrocodone may be the result of metabolism.
 - Hydromorphone from morphine
 - Cone, et al.2 report that hydromorphone may derive from metabolism of morphine.
 - When the free hydromorphone concentration, as a percent of free morphine in a urine specimen, is less than 25 percent, the presence of hydromorphone may be the result of metabolism.
- Note: Refer to the following diagram to aid in clarifying the narratives above regarding the generation of prescription opioids from metabolism.

Figure 1:

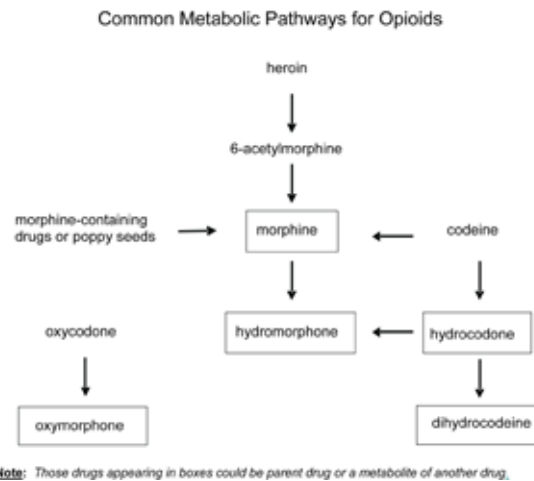


Figure 2:

| Opioids Covered and Cutoff Concentrations (Reporting Limits) Urine, Serum, and Plasma | | |
|--|-----------------------------|------------------------------------|
| Opiates and Related Drugs | Urine Cutoff (ng/mL) | Serum/Plasma Cutoff (ng/mL) |
| Codeine | 5 | 2 |
| Morphine | 5 | 2 |
| Hydrocodone | 5 | 2 |
| Hydromorphone | 5 | 2 |
| Dihydrocodeine (qualitative only) | 5 | 2 |
| Oxycodone | 5 | 2 |
| Oxymorphone | 5 | 2 |
| 6-acetylmorphine (heroin metabolite) | 5 | 2 |
| Methadone and EDDP | 10 | 10 |
| Propoxyphene and norpropoxyphene (norpropoxyphene qualitative only) | 10 | 10 |
| Fentanyl and norfentanyl | 1 | 0.25 |
| Buprenorphine and norbuprenorphine | 5 | 5 |

Related Tests

- Drugs of Abuse 5 Panel, Urine - Screen with Reflex to Confirmation/Quantitation (0092182)
- Drugs of Abuse 5A Panel, Urine - Screen with Reflex to Confirmation/Quantitation (0092183)
- Drugs of Abuse 7 Panel, Urine - Screen with Reflex to Confirmation/Quantitation (0092184)
- Drugs of Abuse 7A Panel, Urine - Screen with Reflex to Confirmation/Quantitation (0092185)
- Drugs of Abuse 9 Panel, Urine - Screen with Reflex to Confirmation/Quantitation (0092186)
- Drugs of Abuse 9A Panel, Urine - Screen with Reflex to Confirmation/Quantitation (0092187)
- Drugs of Abuse 9 Panel, Serum or Plasma - Screen with Reflex to Confirmation/Quantitation (0092420)

References

1. Oyler JM, et al. Identification of hydrocodone in human urine following codeine administration. *J Analytical Toxicology* 2000;24:530-5.
2. Cone EJ, et al. Evidence of morphine metabolism to hydromorphone in pain patients chronically treated with morphine. *J Analytical Toxicology* 2006;30:1-5.
3. Baselt RC. 2004. *Disposition of toxic drugs and chemicals in man*, 7th ed. Foster City, CA: Biomedical Publications.

Test Information

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| 0090364 | Drugs of Abuse Confirmation/Quantitation - Opiates - Urine |
| 0092354 | Drugs of Abuse Confirmation/Quantitation - Opiates - Serum or Plasma |
| 0090362 | Drugs of Abuse Confirmation/Quantitation - Methadone & Metabolite - Urine |
| 0090699 | Drugs of Abuse Confirmation/Quantitation - Methadone & Metabolite - Serum or Plasma |
| 0090368 | Drugs of Abuse Confirmation/Quantitation - Propoxyphene & Metabolite - Urine |
| 0091363 | Drugs of Abuse Confirmation/Quantitation - Propoxyphene & Metabolite - Serum or Plasma |
| 0092570 | Drugs of Abuse Confirmation/Quantitation - Fentanyl & Metabolite - Urine |
| 0092569 | Drugs of Abuse Confirmation/Quantitation - Fentanyl & Metabolite - Serum or Plasma |
| 0093476 | Buprenorphine & Metabolite Quantitation - Total (Conjugated/Unconjugated), Urine |

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.