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POSITION STATEMENT

ACMT Position Statement: Interpretation of Urine Opiate and Opioid Tests

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A positive urine test for opiates or opioids or their metabolites indicates that an agent from the class is present in the body, within the testing limitation of the assay. The results do not identify the dose, route, source, specific timing, or nature of the exposure (e.g., intent). A positive urine test alone does not establish clinical impairment. Management of acute opioid poisoning is based on clinical findings and should not be delayed pending testing results. There is no single universal opioid test, but most clinical immunoassays for opiates have morphine and codeine as their target analytes. Separate assays are required to reliably detect buprenorphine, fentanyl, fentanyl analogs, hydrocodone, methadone, compounds in kratom (mitragynine and 7-hydroxymitragynine), tramadol, oxycodone, U-47700, or other semisynthetic or synthetic opioids structurally distinct from morphine.

Background

Opiates are naturally occurring chemicals derived from the opium poppy that are agonists at opioid receptors (includes morphine and codeine, primarily). The term *opioids* includes opiates and other semisynthetic (e.g., oxycodone) and synthetic chemicals (e.g., fentanyl) that are also agonists at opioid receptors. For regulatory purposes, a "screening test" or "screen" is preliminary, while a "confirmatory test" is considered to be definitive proof of presence in a sample. Screening test results are generally qualitative (reported as "positive" if above previously set cutoff reporting concentration), while confirmatory test results are generally quantitative. Forensic testing refers to application of an assay to answer a legal or employment-related question, while clinical testing refers to application of an assay to patient care. The two commonly used categories of tests are immunoassays and chromatographic tests. Because immunoassays are typically faster and less expensive than chromatographic tests, they are typically used for screening. Although advanced chromatographic methods take longer to perform and are more expensive, they are considered to be the "gold standard," are used as confirmatory tests, and are mandatory in regulated testing.

Clinical Utility of Testing

Urine opioid testing is used to establish whether a drug has been used within a particular window of time. Opioid testing in established healthcare delivery has varied uses, such as to support addiction treatment, pain management, or psychiatric or medical care [1, 2].

The management of patients with acute opioid intoxication should not be based on testing results, but rather based on clinical findings, such as decreased ventilation (breathing). Treatment of opioid toxicity—stimulation, support of the airway, or administration of antidote—should not be delayed for testing results.

A medical toxicologist may be asked whether a test result identifies or excludes exposure or impairment. Urine opioid tests are not designed to determine clinical impairment. Clinical impairment can only be directly determined based

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on observed behavior, signs of somnolence, cognitive function, and motor performance, independent of the presence in urine of an opioid or metabolite alone. In other words, given all of the limits inherent in urine drug testing, particularly variable urine production and concentration and timeline of urine production and collection, there is no predictable correlation between the presence or concentration of an opioid in the urine and the degree of clinical impairment, if any.

Therapeutic Drug Monitoring

Testing for analgesic opioids is often performed in pain management and addiction treatment practice settings. Testing for conventional analgesic opioids, such as hydrocodone or oxycodone (pain management) or methadone and metabolite and buprenorphine and metabolite (addiction treatment), may detect diversion, need for dose increase, rapid metabolizer status, or incorrect self-administration of prescribed medication [1, 2]. Specific qualitative or semi-quantitative assays may be used in an office, and confirmatory testing is generally sent to a reference laboratory. Specimen collection may be observed to assure specimen validity, to detect adulteration, and to hide illicit drugs or addition of therapeutic medication directly to the urine sample in order to hide non-compliance. Measurement of urine specific gravity and creatinine is commonly performed to detect deliberate overhydration or addition of water to the specimen. Other tests may look specifically for adulterants, substances introduced into the specimen for the purpose of interfering with the test results [3].

Federally Regulated Testing

The US Department of Health and Human Services (HHS), the US Department of Transportation, the Federal Aviation Administration, the Department of Defense, Department of Energy, and other agencies have established a drug testing program (commonly called federally regulated testing) to improve workplace safety. The program, which requires detailed procedures for urine collection and specimen handling, is mandated for use in select industries and is voluntarily adopted by certain employers [4].

Federally regulated testing is limited to a few opioids. Screening uses an immunoassay for opioids to identify: morphine, codeine, 6-MAM, hydrocodone, hydromorphone, oxycodone, and oxymorphone [4]. Concentration cutoffs have been determined by a scientific advisory panel (see Table 1). These cutoff levels are regulatory, and not necessarily the same as a given laboratory's limit of detection nor applied in clinical practice.

In federally regulated testing, urine creatinine and specific gravity are also measured to determine if the specimen is too dilute to properly test. If so, a repeat test under observation may be automatically ordered. Other confirmatory steps (e.g., pH, temperature, detection of adulterants such as nitrates) may be taken to assure specimen validity in other venues.

Significance of Positive Urine Test Result

A drug test is reported positive when the analyte concentration exceeds the established reporting threshold or cutoff. Interpretation of the analytical finding is based on the concentration of the analyte in the urine, which is affected by both the extent and duration of exposure, time since last exposure, hydrational status of the subject, and other individual factors. The test results may be accompanied by the sample's specific gravity or, for confirmatory tests, the analyte concentration expressed in comparison to the urinary creatinine to adjust for the urine concentration.

Limitations of Immunoassays

Immunoassays use antibodies to detect the presence of drugs and metabolites. The initial immunoassay opioid screen used in most hospital laboratories is sensitive but not specific and provides a qualitative result only. Therefore, the test result is positive or negative for the drug class, but often not specific

Table.1 Initial test (screening) and confirmatory test cutoffs for opioids in federally regulated urine testing [4].

Initial test analyte	Initial test cutoff	Confirmatory test analyte	Confirmatory test cutoff concentration
Morphine	2000 ng/mL	Codeine Morphine	2000 ng/mL
Hydrocodone/ Hydromorphone	300 ng/mL	Hydrocodone Hydromorphone	100 ng/mL
Oxycodone/ Oxymorphone	100 ng/mL	Oxycodone Oxymorphone	100 ng/mL
6-Acetylmorphine	10 ng/mL	6-Acetylmorphine	10 ng/mL

for the drug within that class (see Table 1). For example, when a cutoff of 300 ng/mL, morphine from dietary poppy seed ingestion may produce a positive test, but it is very unlikely to exceed a cutoff of 2,000 ng/mL. The confirmatory test by gas or liquid chromatography is sensitive, specific, and quantitative. Confirmatory tests are typically "send out" tests, and results aren't readily available in the clinical environment.

Urine immunoassays may be used alone in the clinical setting but should be followed by chromatographic confirmation when employed for forensic, regulatory, legal, or high-consequence clinical purposes. Historically, urine immunoassays for morphine metabolites have been the most common opioid assays used in the clinical setting. These tests detect morphine, and, indirectly, codeine and diacetylmorphine (heroin, which is metabolized first to 6-acetylmorphine), which are both ultimately metabolized to morphine [5].

Separate immunoassays are needed to identify the presence of oxycodone and hydrocodone, buprenorphine, methadone, tramadol, and fentanyl (and its analogs), drugs that are not included on the typical "5-panel" and "10-panel" screens. None of the above opioid immunoassays detects U-47700, methadone, tramadol, fentanyl (and its analogs), or compounds found in kratom (mitragynine and 7-hydroxymitragynine), all of which bind the mu-opioid receptor despite distinct chemical structures. Importantly, given the presence of fentanyl and related analogs in the illicit and counterfeit drug supply, a negative test result on an immunoassay not specific for fentanyl cannot be used to exclude fentanyl or opioid exposure or intoxication. Urine fentanyl immunoassays detect many, but not all, fentanyl analogs [6, 7].

Opioid immunoassays may also detect morphine and codeine found in poppy seeds. Opioid cutoffs are typically set sufficiently high that consuming foods with poppy seeds will not elicit a positive result except in those with exceedingly high consumption. Individuals with such large exposure (for example from a poppy seed tea) may experience clinically significant opioid agonist effects and produce a urine specimen morphine concentration above the cutoff [8]. Detecting heroin metabolite 6-monoacetyl morphine with a specific assay would differentiate poppy seed from heroin use since humans do not acetylate morphine to this metabolite.

False-Positive Immunoassay Results

Because immunoassays use antibodies chosen to detect a specific epitope (antigenic region) of a compound, certain non-opioid drugs with antibody cross-reactivity can cause false-positive immunoassay results. These false positives are concentration-dependent and not necessarily generalizable across different manufacturers' assays. This correlation is not consistent across assays, however, and some patients with clinical intoxication from these opioids will still have negative opioid immunoassay results.

However, certain immunoassay results may be falsely positive due to non-opioid agonists such as fluoroquinolone antibiotics and, rarely, the opioid antagonist naloxone due to their structural similarity to morphine [9, 10]. Consulting the laboratory, a medical toxicologist, medical review officer, or the assay user manual may help clarify an unexpected immunoassay result. If a definitive answer is needed in a specific situation, confirmation with an advanced chromatographic method can be performed.

Conclusion

The interpretation of urine tests results for opioid use requires an understanding of their limitations. Urine opioid assays, particularly when confirmed by chromatography, indicate the introduction of a drug into the body prior to specimen collection. Most clinical opioid screening immunoassays detect morphine, and indirectly, codeine and diacetylmorphine (heroin). Separate assays are required to reliably detect buprenorphine, fentanyl, fentanyl analogs, hydrocodone, methadone, compounds in kratom, tramadol, oxycodone, U-47700, or other semisynthetic or synthetic opioids. Some of these may be included in hospital testing, but are often not included in typical "5-panel" or "10-panel" testing. Urine assays are not designed to determine impairment. Management of acute opioid intoxication is based on clinical findings and should not be delayed for testing results.

Disclaimer

While individual practices may differ, this is the position of the American College of Medical Toxicology at the time written, after a review of the issue and pertinent literature.

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Declarations

Conflicts of Interest None.

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