Toxicologic Testing for Opiates: Understanding False-Positive and False-Negative Test Results

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LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Dr Stern is an employee of the Academy of Psychosomatic Medicine, has served on the speaker's board of Reed Elsevier, and has received royalties from Mosby/Elsevier and McGraw Hill. **Dr Moran** is a stock shareholder in Eli Lilly, Johnson & Johnson, and Merck. **Drs Keary, Wang,** and **Zayas** report no financial or other affiliations related to the subject of this article.

Prim Care Companion CNS Disord 2012;14(4):doi:10.4088/PCC.12f01371

Submitted: *February 28, 2012; accepted April 24, 2012.*
Published online: *July 26, 2012.*
Funding/support: *None reported.*
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Have you ever had a patient who insisted that he or she was neither using nor abusing opiates when the toxicology screen was positive? Have you ever been perplexed by not knowing whether to believe your patient or the laboratory test? Have you ever considered if certain medications or foods can contribute to false-positive or false-negative drug screens?

If you have, then the following case vignette and discussion should serve as a stimulus for further inquiry into these and other questions.

CASE VIGNETTE

Mr A, a 30-year-old man with a history of *S. anginosus* mitral and aortic valve infective endocarditis (secondary to intravenous [IV] drug abuse), had both his mitral and aortic valves replaced; he subsequently developed *Enterococcus faecalis* bacteremia. Several months later while on an indefinite course of amoxicillin/ciprofloxacin prophylaxis, Mr A arrived at the emergency department complaining of fever, back pain, and weakness in the setting of a relapse of IV heroin use; he had not been taking his antibiotics for the previous 4 days. Initially, 4 of 4 blood cultures revealed α-hemolytic strep, and Mr A was admitted to the hospital for IV antibiotics. Cardiac imaging studies showed thickening of his prosthetic valves consistent with endocarditis, and an echolucency was suggestive of an aortic root suture line dehiscence. Consultants from the cardiology and cardiothoracic surgery departments concluded that reconstruction was not a viable option given his cardiac anatomy and the difficulties he had experienced during his valve replacement surgery. Conservative treatment was pursued. Mr A was started on IV antibiotics (vancomycin, ampicillin, and streptomycin); these treatments were switched to IV penicillin and gentamycin on hospital day 2 after susceptibility data were reviewed. His other medications included gabapentin (600 mg 3 times a day) and multivitamins. On admission to the hospital, Mr A's urine toxicologic screen was positive for opiates, and he admitted to heroin usage on the day of presentation.

On the night of admission, Mr A complained of opiate withdrawal symptoms. At the recommendation of the psychiatric consultant, he was started on methadone to be followed by a 5-day methadone taper (methadone 30 mg on day 1, tapering to methadone 5 mg in the morning on hospital day 5). On hospital day 4, Mr A was suspected of using nonprescribed narcotics with another patient (a known IV drug user) on the unit; staff reported that Mr A locked himself in the bathroom for 10 minutes, after which a syringe was found in the toilet. Mr A adamantly denied using IV narcotics, and he stated that he had found the empty syringe in his belongings; he had attempted to flush it down the toilet, fearing that, if discovered, staff would accuse him of using it while in the hospital.

Given the staff's suspicion of Mr A's illicit drug use, daily urine toxicologic screens were obtained until the day of discharge. Urine opiates that do not cross-react with urine methadone were positive on hospital days 4 and 5 and negative on all subsequent days. Daily urine toxicologic screens specific for methadone remained positive throughout admission. The treatment team interpreted the positive urine opiate screen as evidence of surreptitious use. As a safety measure, Mr A was switched to a single room at the end of the corridor and his visitor privileges were rescinded, a move that he protested heavily, stating that it unfairly deprived him of the chance to interact with loved ones at the most trying time of his life. A urine 6-monoacetylmorphine

Clinical Points

- Drug testing has become widespread in clinical settings and elsewhere (eg, the workplace, the military, in professional sports, and in forensic settings).
- Enzyme-mediated immunoassays (EIAs) use antibodies to specific opiates that bind to that opiate when present in a sample to produce a measurable reaction, while gas chromatography that separates different molecules in a sample is often followed by mass spectroscopy that compares spectrographic patterns to a standard to identify a separated molecule.
- False-positive screens are the result of cross-reactivity to the antibody in EIA tests due to specific medications or direct binding to the antibody due to inadvertent ingestion of opiates (eg, poppy seeds) or use of medications (eg, quinolones, rifampin, verapamil, quetiapine, and diphenhydramine), as well as by interference caused by lactate dehydrogenase and lactate.

(6-MAM; a short-lived metabolite of heroin) screen was later requested to enhance diagnostic certainty. The urine sample was negative for the metabolite on hospital day 4, as were all subsequent samples, creating disagreement among the team about whether the patient truly had been using heroin while hospitalized. Mr A was discharged in a stable medical condition to a rehabilitation facility for continued IV antibiotics on hospital day 8.

WHAT TYPES OF DRUG SCREENS ARE EMPLOYED TO DETECT OPIATES?

Drug testing has become widespread in clinical settings and elsewhere (eg, the workplace, the military, in professional sports, in forensic settings). Because many drug tests are both quick and simple, the assays are often less than perfect, leading to false-positive and false-negative results. Therefore, it is imperative that clinicians who review results of drug tests understand the limitations of these tests and use both objective and clinical data to interpret the results appropriately.

Drug screening can be conducted on urine, blood, hair, saliva, sweat, and nails. However, urine is the most commonly used specimen in drug testing across clinical sites given its ease of collection and rapid analysis. In addition, the concentration of drug metabolites in the urine tends to be higher than those of serum samples.[1]

The 2 categories of commonly used toxicology tests are antibody-based immunoassays (usually an enzyme-mediated immunoassay [EIA]) and specific drug identification tests (such as gas chromatography–mass spectroscopy [GC-MS]). EIA tests utilize antibodies to specific opiates that bind to that opiate when present in a sample to produce a measurable reaction. These tests have the advantages of decreased cost and excellent sensitivity[2] and are readily available in both hospitals and clinics. However, while the tests are quick and relatively easy to use, their specificity is limited by cross-reactivity and, consequently, can result in false-positive results.

The second category of tests allows for specific drug identification using gas chromatography (GC) (used to separate different molecules in a sample) followed by mass spectroscopy (MS) (wherein spectrographic patterns are compared to a standard to identify the separated molecule). GC-MS is considered the gold standard for confirmatory testing; it allows for quantification and identification of drugs and their metabolites, with sensitivities and specificities of 99%.[3] While GC-MS is highly accurate, it is time-consuming and requires a higher level of expertise to perform than immunoassays. For these reasons, GC-MS is more expensive and less available and is usually performed only after a positive EIA test result has been obtained.

When interpreting results from these tests, knowledge of the synthetic properties of the opiates and their metabolites is important. Standard EIA tests contain antibodies for naturally occurring morphine and are less likely to bind to synthetic and semisynthetic opiates. For example, in 1 study of 52 standard EIA urine tests for opiates (as compared to GC-MS studies on the same sample), oxycodone was detected only 12% of the time.[3] Semisynthetic opiates (oxycodone, hydromorphone, oxymorphone, levorphanol, buprenorphine) and purely synthetic opiates (fentanyl, methadone, propoxyphene, meperidine, tramadol, pentazocine) have their own specifically designed EIA tests that usually need to be specially requested if testing in the inpatient environment. Furthermore, the metabolism of these opiates may result in misleading results. A study of clinicians who use urine toxicology testing in their practice revealed that the majority were not aware of morphine as a common metabolite of codeine, which may lead to false accusations of illicit opiate use.[4]

WHAT CAUSES FALSE-POSITIVE URINE TOXICOLOGY SCREENS AND HOW CAN THEY BE DETECTED?

False-positive screens are the result of cross-reactivity to the antibody in EIA tests due to specific medications or direct binding to the antibody due to inadvertent ingestion of opiates (eg, poppy seeds). Medications common to the inpatient setting (eg, quinolone antibiotics, rifampin) can also result in false-positives on opiate EIA testing.[5] In addition, there are a wide variety of common medications (eg, verapamil, quetiapine, diphenhydramine, doxylamine) that are known to give false-positive results on methadone-specific EIA testing.[6,7] Poppy seeds can readily result in a positive finding in standard urine EIA testing; a product of the opium poppy, these seeds contain small amounts of codeine and morphine. One study found morphine levels

high enough to result in positive EIA testing after ingestion of 1 poppy seed muffin or 2 poppy seed bagels.[8] This type of false-positive result is much less common in testing outside of clinical situations (eg, the workplace), wherein thresholds for a positive opiate screening are higher.[9] A careful history for medications or food that can induce a false-positive result should be performed and, if present, GC-MS testing should be used to distinguish between the presence of true opiates and false-positive results.

A coincidental false-positive test could also result from the way in which lactate dehydrogenase and lactate interfere with assays for commonly abused substances such as opiates.[10] Hence, urine from a patient who is at risk for lactic acidosis (eg, one with diabetes mellitus, liver disease, or a toxin ingestion) should undergo additional confirmatory testing.

The specific detection of heroin as separate from other opiates is facilitated by its unique metabolites. Heroin is a semisynthetic opiate that by virtue of its metabolism to morphine produces a positive result on standard EIA tests. Morphine is then further metabolized to morphine-3-glucuronide and morphine-6-glucuronide before excretion (primarily via the kidneys). However, prior to its metabolism to morphine and subsequent glucuronidation, heroin is rapidly metabolized to 6-MAM. Because 6-MAM is the first product of heroin metabolism, no other compound produces this metabolite, and its presence is unequivocal confirmation of heroin usage. Importantly, 6-MAM is known to have a short half-life and is thought to be detectable by specified EIA or GC-MS only up to 12 hours after ingestion.[11,12]

In situations in which a patient is taking a prescribed opiate as well as an illicit opiate, physicians must be especially careful when interpreting test results. Opiate abuse by opiate-treated chronic pain patients is common[13] and can complicate interpretation of opiate testing. For example, since both codeine and heroin have morphine as a metabolite, mistaken accusations of morphine or heroin abuse may arise in patients prescribed codeine. Differentiation between the 2 drugs can be challenging when 6-MAM testing is not available and, in such a case, clinicians should consult with laboratory hospital staff to determine whether additional specific EIA tests or GC-MS testing would be warranted.

WHAT CAUSES FALSE-NEGATIVE URINE TOXICOLOGY SCREENS AND HOW CAN THEY BE DETECTED?

Two common potential causes for false-negative opiate tests are using the wrong test for a specific opiate and having an insufficient concentration of an opiate in the sample. Clinicians may minimize such errors by keeping in mind the specific opiates being tested for. Most of the above-mentioned semisynthetic and synthetic opiates have their own standardized EIAs with excellent sensitivities,[14] some of which may be a part of a hospital's standard toxicology screen. All physicians should be aware of which EIA tests are part of their hospital's standard toxicology screen and the potential need to specifically request EIA tests for synthetic opiates. Concentration of a substrate in a sample is dependent upon a drug's individualized absorption and metabolism rates as well as on the drug's pharmacokinetics. Toxicology tests are designed with cutoff concentrations in mind; these cutoffs represent the lowest possible concentration that will produce a positive test result. These tests are calibrated to detect opiates taken within 1 to 3 days in the majority of individuals[15]; however, individual variation that is based on metabolic genotype (eg, ultrafast metabolizers) should be considered.

Individuals falsify drug tests to induce false-negative results through a variety of methods: via manually tampering with the sample (eg, by adding a masking agent or water), by substitution (eg, by using urine bought from clean sources off the Internet), or by dilution (eg, ingesting a substantial amount of water or using commercially available detoxification kits). A number of techniques are employed by laboratories to identify tampered specimens.

In the case in which an individual tampers with a urine sample via a masking agent, the intention is to interfere with the detection of a drug or its metabolite. The masking agent can be a household product (such as bleach or vinegar) or a commercially available compound (such as sodium or potassium nitrate or peroxide/peroxidase). Laboratories attempt to detect such alterations by noting the color and appearance of the specimen and will shake it to assess for bubbles or foam that may suggest the presence of soap, ammonia, hydrogen peroxide, or bleach. When individuals attempt to substitute their urine sample with clean urine (obtained commercially or from a friend), this may be detected via temperature recording that some laboratories obtain within 4 minutes of collection. Finally, a wide variety of commercial detoxification products exist that use frequent ingestion of water or herbal supplements that promise to aid with avoidance of detection. Dilution of the urine is detected through measurement of urine creatinine and assessment of the urine color, which will also detect direct addition of water to the sample following micturation. Detoxification kits will sometimes add vitamin B compounds to normalize urine color or creatine to offset the laboratories' precautions; however, safety concerns exist with this type of alteration, most notably electrolyte abnormalities induced by ingestion of large amounts of water.[16]

Patients on buprenorphine maintenance are often screened at clinics to ensure adherence to buprenorphine and to detect relapse. Addicts who sell their prescriptions are motivated to adulterate their urine samples to test positive for buprenorphine, which can be accomplished by crushing buprenorphine and adding it directly to the sample. Of note, this method often contaminates the next urine sample analyzed, as residue is often left on the probes of the machines that analyze the samples.

WHAT ARE THE RISKS AND BENEFITS OF DOUBTING PATIENTS?

Insistence on opiate testing often highlights mistrust between patients and their physicians. Although some physicians believe that they have a moral obligation to trust their patients (to strengthen the therapeutic relationship and to support patient autonomy),[16,17] others favor rigorous inquiries to enhance optimal treatment. Other physicians believe that vigilance and drug testing are necessary to safeguard access to a variety of limited resources. While physicians' trustworthiness has been the recent target of medical ethics, physicians' trust of patients has received less scrutiny.[18] Nevertheless, the presence or absence of such trust has important consequences, and the subject warrants thoughtful discussion.

Physicians often perceive that their skepticism (and ordering of drug testing) is necessary to establish diagnostic certainty; it allows them to go beyond reliance on subjective reporting that can be embellished for secondary gain or be colored by a patient's personality.[16] Yet, the inherent danger of doubting a patient's self-reported history is the creation of diagnostic inaccuracy (the very thing that the physician is trying to avoid). Physicians tend to have more difficulty believing a patient with unusual symptoms or an illness course that fails to fit a well-established pattern; such distrust may lead to meaningful symptoms being discounted, delayed, dismissed (as trivial), incorrectly diagnosed, and/or inadequately treated.[16]

Physicians are trained to think critically and objectively, often buoyed by knowledge of laboratory tests and other aspects of the diagnostic workup. Lack of trust toward particular patients and patient populations (eg, those with substance abuse) often results in more frequent monitoring (eg, with serum/urine toxicity screens, that in turn, increase patient burden and overall health care costs). Frequent monitoring also serves as an ongoing reminder to patients of the uneven power dynamic inherent in the physician-patient relationship.[17]

Trust is a dynamic and reciprocal process. A physician's trust in a patient may enhance the patient's trust in the physician, while the lack of physician trust is perceived negatively by many patients and may, in turn, adversely affect a patient's behavior.[19,20] This lack of trust could be manifest by nonadherence with treatment recommendations, by missing appointments, or by an unwillingness to openly and accurately describe symptoms; each of these behaviors perpetuates and erodes the doctor-patient alliance.[20] Moreover, future treatments can be jeopardized if a physician's skepticism is documented in the medical record (allowing it to be easily accessed and referenced by others).

All of these concerns must be balanced against the risks (eg, slipping into dangerous waters with the patient and partaking in an uneven sense of responsibility in the therapeutic relationship) of the overly-trusting clinician. Surreptitious use of medications or illicit drugs is an example of a "real-life" clinical situation that can place the patient at risk of oversedation or untoward drug-drug interactions. Moreover, abuses of the medical system are a valid concern for physicians to whom society is increasingly looking to act as gatekeepers for progressively strained medical resources. Finally, when confrontation is assiduously avoided by the clinician it can contribute to an imbalance in the therapeutic relationship (the patient expects care without reliably demonstrating healthy decision-making). This imbalance may ultimately disempower the patient and limit his or her sense of responsibility (regarding their health care) and can contribute to powerlessness on the part of the clinician.[21,22]

CASE DISCUSSION

Conflicting results on urine opiate testing complicated the care of Mr A, who was suspected of using heroin while hospitalized for treatment of his endocarditis. Mr A had positive screening for opiates by day 4 of hospitalization in the absence of medications or foods that can produce a false-positive result. However, Mr A had negative testing of heroin-specific metabolites, which would have allowed for confirmation of the suspected surreptitious use. One possibility is that Mr A had indeed been using heroin in the hospital, and the 6-MAM screen was assessed outside of the window for testing. It is less likely, but theoretically possible, that ciprofloxacin taken intermittently as an outpatient was still present in Mr A's system in sufficient quantities to induce a false-positive result. Urine GC-MS testing for the presence and concentration of morphine could have confirmed heroin use and, if the concentration was high enough, whether it had been used recently. The conflicting results led to disagreement among members of the team, some of whom felt that Mr A was being wrongly accused. Accusations against the patient had significant consequences in creating an adversarial doctor-patient relationship and altering his treatment options. Further knowledge regarding toxicologic screening tests would have gone a long way toward guiding treatment and would have helped unify the team around setting limits as necessary.

CONCLUSION

A deeper understanding of toxicology testing, including common sources of false-positives and false-negatives, can help clarify conflicting results and allow for interventions with patients that preserve the doctor-patient relationship. Careful usage and accurate interpretation of toxicology testing in light of its limitations allow for judicious and therapeutic confrontation when illicit drug use is confirmed. Conversely, a lack of trust toward a patient can lead to inadequate/inappropriate treatments, erosion of the doctor-patient relationship, and even inaccurate diagnoses. The consequences of this lack of trust include patient behaviors that further jeopardize treatment and weaken the doctor-patient alliance, while increasing monitoring and health

care costs. Physicians must bear in mind the already uneven power dynamic between them and their patients; distrust shifts the balance of power even further toward the physician and leaves the patient feeling more vulnerable.

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