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Interpretation of Urine Drug Screens
Metabolites and Impurities

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A 50-year-old woman with chronic pain and recurrent infections from common variable immunodeficiency presented to a new primary care physician for management of her pain medications. Her pain was related to multiple vertebral fractures due to chronic steroid use for an inflammatory polyarthritis that was not responsive to hydroxychloriquine and methotrexate. Her pain medication regimen (methadone, 20 mg [3×/d]; immediate-release morphine, 30 mg [5×/d]; gabapentin, 1200 mg [2×/d]; duloxetine, 60 mg/d; and celecoxib, 200 mg [2×/d]) helped her independently complete instrumental activities of daily living. She reported no adverse effects (eg, somnolence or constipation). A comprehensive urine drug screen using immunoassay and mass spectrometry was ordered (**Table 1**).

HOW WOULD YOU INTERPRET THESE RESULTS?

A. The patient is taking methadone and morphine.

B. The patient is taking methadone and codeine.

C. The patient is taking methadone, hydromorphone, and codeine.

D. The patient is taking methadone, morphine, hydromorphone, and codeine.

Table 1. Laboratory Test Results

Test Performed	Method of Detection	Patient Values (Qualitative)	Patient Values, ng/mL	Assay Cutoff, ng/mL
Opiates	Immunoassay	Positive	>800	50
Codeine	Mass spectrometry	Positive	254	100
Morphine	Mass spectrometry	Positive	>50 000	100
Hydrocodone	Mass spectrometry	Negative		100
Hydromorphone	Mass spectrometry	Positive	5792	100
Norhydrocodone	Mass spectrometry	Negative		100
Oxycodone	Mass spectrometry	Negative		100
Fentanyl	Mass spectrometry	Negative		3
Methadone	Immunoassay	Positive	>500	130
Methadone	Mass spectrometry	Positive	2911	100

Answer

A. The patient is taking methadone and morphine.

Test Characteristics

With the increasing opioid dependence epidemic, clinicians must monitor the use of prescription opioids to identify misuse, addiction, and diversion (ie, selling or distributing prescribed medications). Urine drug screens can confirm whether patients on chronic opioids are using prescribed drugs and abstaining from illicit substances. Occasionally, it can be difficult to interpret a result as normal or abnormal based on the metabolites found in the urine.

Mass spectrometry–based methods of detection can identify and quantify multiple drugs and metabolites simultaneously. Additionally, mass spectrometry can measure very low concentrations of excreted drugs and detect minor metabolites and impurities not quantifiable with immunoassays. Medicare midpoint reimbursements for mass spectrometry–based tests range from $158.98 to $343.07, depending on the number of drug classes being tested.[1]

Accurate interpretation of drug screen results requires knowledge of the urine metabolites (**Table 2**).[2-6] Some opioids produce metabolites chemically identical to other opioid medications, which may complicate the interpretation. Codeine, for example, is a prodrug that metabolizes to morphine in most patients.[2]

Application of Test Results to This Patient

Urine drug screen results showed the expected morphine and methadone but also hydromorphone and codeine. Hydromorphone is a minor metabolite of morphine (found at ≤10% of the morphine urine concentration)[7] that can be seen in patients prescribed higher daily doses of morphine and detected when morphine concentrations reach 10 000 ng/mL on assay.[7] Codeine is not a metabolite of morphine, but it can be an impurity in the production of morphine (estimated at 0.04%-0.5% of the concentration of morphine).[4] The patient's hydromorphone and codeine urine concentrations are consistent with these findings. It is possible that the patient had an additional source of hydromorphone or codeine, which cannot be determined from the urine result. If concentrations were higher than the 10% or 0.5% of the morphine concentration, the patient could be taking hydromorphone or codeine.

What Are Alternative Diagnostic Testing Approaches?

Screens using only immunoassay for common drugs of abuse are an alternative to mass spectrometry–based screens designed for pain management. Immunoassay methods are less expensive (Medicare reimbursement range, $20.22- $107.85)[1] and allow physicians to quickly determine whether commonly abused drugs are absent and whether opiates are present; however, they are subject to false-positive and false-negative results, which vary based on the drug, drug class, and the assay used. Most semisynthetic opioids

Table 2. Commonly Prescribed and Abused Opioids and Metabolites/Contaminants

Opioid	Urine Metabolites	Contaminants	Comments
Codeine	Morphine; hydrocodone (<10%); norcodeine	None	Codeine is metabolized to morphine so both may be present[2]
Heroin	6-Monoacetylmorphine; morphine; normorphine	Codeine (if heroin is contaminated with acetylcodeine)[3]	Because the half-life for 6-monoacetylmorphine is 8 hours, morphine may be the only compound detected after heroin use[3]
Morphine	Normorphine; hydromorphone (<10%); morphine-6-glucuronide; morphine-3-glucuronide	Codeine	Codeine is a pharmaceutical contaminant of morphine at 0.04%-0.5% of the morphine concentration[4]
Hydrocodone	Hydromorphone; norhydrocodone; dihydrocodeine	None	Hydrocodone is metabolized in small amounts to hydromorphone so both may be present[5]
Hydromorphone	Hydromorphone-3-glucuronide	None	
Oxycodone	Oxymorphone; noroxycodone	Hydrocodone	Hydrocodone is a pharmaceutical contaminant of oxycodone at < 0.1% of the concentration of oxycodone[6]; oxycodone is metabolized to oxymorphone so both may be present[5]
Oxymorphone	Oxymorphone-3-glucuronide; 6-hydroxy-oxymorphone	None	
Fentanyl	Norfentanyl	None	
Methadone	2-Ethylidene-1; 5-dimethyl-3; 3-diphenylpyrrolidine	None	
Buprenorphine	Norbuprenorphine	None	

(ie, hydrocodone, oxycodone) and synthetic opioids (ie, fentanyl, methadone) are not reliably detected by an immunoassay designed to detect opiates. Immunoassays specifically designed to detect oxycodone show sensitivities and specificities at approximately 99%, while those specifically designed to detect synthetic opioids are approximately 95%.[8] Mass spectrometry is used to confirm immunoassay results and has been recently advocated as a first-line test in chronic pain management.[8]

Patient Outcome

After contacting her prior physician and reviewing the prescription drug-monitoring program (a statewide electronic database that collects information on dispensed controlled substances), there was no concern for misuse or abuse. An opioid consent and contract,[9] which detailed the risks and benefits of opioid therapy and outlined expectations of the patient, was reviewed and signed by the patient. Although her daily opioid dosage was greater than 200 morphine milligram equivalents, the benefit of pain control that promotes independence was considered to outweigh the potential harms of therapy. The regimen was continued with a plan for a multidisciplinary approach to treating her pain and slowly tapering the opioids.

Clinical Bottom Line

- Urine drug screens give reproducible objective data and are effective for monitoring opioid use in chronic pain management.
- Opioid contracts can provide structure and support for the patient and physician—discuss at the initiation of therapy.
- Hydromorphone can be found as a metabolite in patients on high-dose long-term morphine treatment.[7]
- Codeine can be an impurity in the production of morphine (range, 0.04%-0.5%) of the concentration of morphine.[4]

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