HealthPartners®
Institute for Medical Education

Interpretation of Opiate Urine Drug Screens

Summary

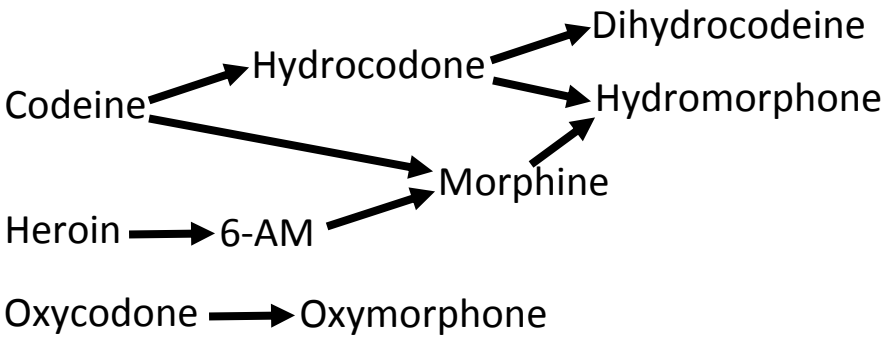
- Urine drug testing is highly reliable, but false positives can rarely occur for some drugs. As always, clinical judgment is necessary when interpreting test results.
- The length of time a drug can be detected in the urine varies due to several factors, including hydration, dosing, metabolism, body mass, urine pH, duration of use, and a drug's particular pharmacokinetics. (See table below for some "average" times for different drugs.)

Length of Time Drugs of Abuse Can Be Detected in UrineDrug	Time
Alcohol	7-12 h
Amphetamine	48 h
Methamphetamine	48 h
Barbiturate	
Short-acting (eg, pentobarbital)	24 h
Long-acting (eg, phenobarbitol)	3 wk
Benzodiazepine	
Short-acting (eg, lorazepam)	3 d
Long-acting (eg, diazepam)	30 d
Cocaine metabolites	2-4 d
Marijuana	
Single use	3 d
Moderate use (4 times/wk)	5-7 d
Daily use	10-15 d
Long-term heavy smoker	30 d
Opioids	
Codeine	48 h
Heroin (detected as morphine)	48 h
Hydromorphone	2-4 d
Methadone	3 d
Morphine	48-72 h
Oxycodone	2-4 d
Propoxyphene	6-48 h
Phencyclidine	8 d

-- Mayo Clinic Proc. 2008; 83(1)66-76

- Sometimes the specific drug ingested is not detected, but instead one of its metabolites is found.

Opiate/Opioid Metabolism



- Two types of urine drug tests are used for HealthPartners patients – immunoassay and gas chromatography-mass spectrometry (GC/MS).
- The first test done is the immunoassay. This can be susceptible to false positives, so when a positive result is obtained it is confirmed by GC/MS.or the pain management urine drug screen,/MS is done for these drugs regardless of the immunoassay screen result: morphine, codeine, oxycodone, oxymorphone, hydrocodone, hydromorphone. The GC/MS confirmation assays are highly reliable and specific tests with very rare interferences.
- Fentanyl (Duragesic) is not easily detected in either urine or serum. Our current system does not allow accurate determination of the presence of this drug. HealthPartners may purchase new equipment that will make this possible within the next year. Until that happens, you will not be able to tell whether a patient is using fentanyl (Duragesic patches) based on the results of the urine drug screen.

Discussion

Current urine drug testing methods were designed to identify illicit use of drugs in the forensic or occupational setting. In this setting, high specificity was needed to avoid a false positive result and this was carried out by using a relatively high cutoff concentration needed to trigger a positive result. In the setting of pain management compliance testing, both drug pharmacokinetics (how the body acts on a drug) and testing limitations that affect the results of urine testing must be understood for proper interpretation.

Although the name “opiate” is often used to describe any member of the class of drugs that acts on opioid receptors, the term “opiate” properly refers to the natural alkaloids found in opium poppy resin (*Papaver somniferum*), which include morphine, codeine and thebaine. The term “opioid” refers to the synthetic and semi-synthetic opioid receptor drugs, including heroin, hydromorphone, hydrocodone, oxycodone, oxymorphone, buprenorphine, fentanyl, and methadone.

Drug	Half-life (hr)	Metabolites	Concentrations above the cutoff will screen positive for
morphine	1.5 - 6.5	normorphine, **hydromorphone (<2.5%)**	Opiates
codeine	1 - 4	**morphine**, **hydrocodone (<11%)**, norcodeine	Opiates
oxycodone	4 - 12	**oxymorphone**, noroxycodone	Oxycodone
oxymorphone	3 - 6	6-hydroxy-oxymorphone	Oxycodone
hydrocodone	3.5 - 9	**hydromorphone**, norhydrocodone, **dihydrocodeine**	Opiates
hydromorphone	3 - 9	hydromorphol	Opiates

* **bolded** metabolites are identical to pharmaceutically available drugs

Assay Technologies

The pain management urine drug screen offered within the HealthPartners Family of Care consists of two steps. First, a qualitative (positive/negative) immunoassay screen is completed, including tests for opiates (300 ng/mL cutoff), oxycodone (100 ng/mL cutoff), amphetamine, barbiturate, benzodiazepines, cocaine, methadone, PCP, propoxyphene, and THC. These drugs are reported as positive if they are present at a concentration above the designated cutoff (see Regions Hospital Laboratory Toxicology website on *myPartner* for specific cutoffs and drugs detected) and confirmed as positive by GC/MS. For the pain management panel only, regardless of the screen results, GC/MS confirmation for the following drugs are completed and reported individually as positive/negative with a detection limit of 100 ng/mL: morphine, codeine, oxycodone, oxymorphone, hydrocodone, hydromorphone. This allows for higher sensitivity and specificity along with offering results for each drug individually.

In general, immunoassay technologies are susceptible to interfering substances (false positives) and cross-reactivity (true positives for non-target drugs, due to structural similarity) to varying degrees. Accordingly, each result needs to be interpreted in the context of the clinical picture and in conjunction with our confirmatory method of gas chromatography/mass spectrometry (GC/MS). The immunoassay for opiates is primarily targeted to detecting morphine, hydrocodone, dihydrocodeine, codeine, 6-acetylmorphine (metabolite of heroin), and hydromorphone. Due to that assay's insensitivity for oxycodone, the oxycodone assay is utilized to detect oxycodone and oxymorphone. The GC/MS confirmation assays are highly reliable and specific tests with very rare interferences.

Detection Windows

The window to detect the presence of a particular drug in a person's urine is highly dependent on multiple factors, such as:

- **Hydration** - More dilute urine from high fluid intake may cause dilution of drug and therefore a negative result due to levels present but below the cutoff. Conversely, a patient may greatly reduce fluid intake in order to concentrate their urine when trying to mask inappropriate reduced intake of their prescribed drug.

- **Dosing** - If a patient is on a low dose or has a long interval between doses, the level of drug in their urine may be too low to be detected by the immunoassay or confirmation assay, i.e. below the cutoff. Similarly, the time between the last dose of a drug taken and the collection of the urine specimen may affect if the drug is present at concentrations adequate to produce a positive result.

- **Metabolism** - Metabolism is unique to each individual, determined by genetic and environmental factors. Genetic polymorphisms of the CYP450 2D6 enzyme can cause individuals to be poor or rapid metabolizers of opioids and other drugs metabolized by those enzymes[1]. Additionally, environmental influences further complicate metabolism. For example, co-administered drugs that are also metabolized by CYP450 enzymes used by the opioids or that inhibit CYP450 2D6 cause decreased metabolism, see Table below. Conversely, rifampin and dexamethasone are known to induce CYP450 2D6, causing increased metabolism of opioids with a resulting shortened detection window. Other factors affecting metabolism include age, sex, ethnicity, and renal or liver impairment.

TABLE 3. **Cytochrome P450 2D6 Substrates, Inhibitors, and Inducers**

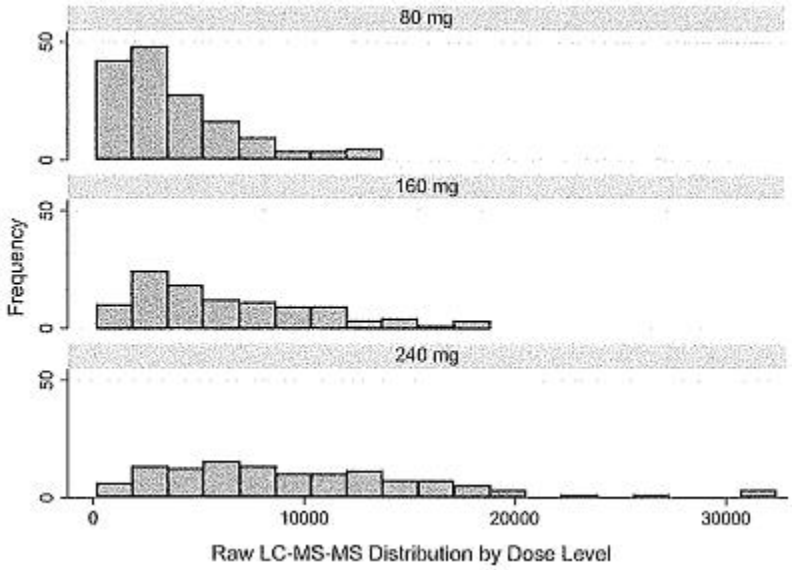
Substrates		Inhibitors		Inducers
Antiarrhythmic agents	*SSRIs*	*Antiarrhythmic agents*	*Antihistamine*	*Antibiotic*
Encainide	Fluoxetine	Amiodarone	Chlorpheniramine	Rifampin
Flecainide	Fluvoxamine	Quinidine	*Histamine H_2 receptor antagonists*	*Glucocorticoid*
Lidocaine	Paroxetine	*Antipsychotic agents*	Cimetidine	Dexamethasone
Mexiletine	*Tricyclics*	Chlorpromazine	Ranitidine	
Propafenone	Amitriptyline	Reduced haloperidol	*Other drugs*	
Sparteine	Amoxapine	Levomepromazine	Celecoxib	
β-Blockers	Clomipramine	*SNRI*	Doxorubicin	
Alprenolol	Desipramine	Duloxetine	Ritonavir	
Carvedilol	Doxepin	*SSRIs*	Terbinafine	
Metoprolol	Imipramine	Citalopram		
Propranolol	Nortriptyline	Escitalopram		
Timolol	*Other drugs*	Fluoxetine		
Antipsychotic agents	Amphetamine	Paroxetine		
Aripiprazole	Chlorpheniramine	Sertraline		
Haloperidol	Debrisoquine	*Tricyclic*		
Perphenazine	Dextromethorphan	Clomipramine		
Risperidone	*Histamine H_1 receptor antagonists*	*Other antidepressant/ antianxiolytic agents*		
Thioridazine	Metoclopramide	Bupropion		
Zuclopenthixol	Phenformin	Moclobemide		
SNRIs	Tamoxifen			
Duloxetine				
Venlafaxine				

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
From Indiana University School of Medicine,[28] with permission.

Other Factors

The detection window of a drug is also affected by: duration of use, body mass, urine pH and a drug's particular chemistry, i.e. half-life and volume of distribution. If a negative result is obtained for a drug prescribed to the patient, the entire clinical picture must be taken into consideration to determine if the patient was: 1) not taking the drug, 2) taking a lower dose than instructed, or 3) taking the drug properly but the results were negative due to one of above factors. Similarly, if a positive result is obtained for a drug not prescribed to the patient, the entire clinical picture must be taken into consideration to determine if the patient was taking the non-prescribed drug, has a false positive result (applies to immunoassay only) or if the drug is simply a metabolite of a prescribed drug (as applicable).

The following figure exemplifies the amount of variation possible in the concentration of drug present in individuals taking the same dose of a drug[2]. In this example, 36 healthy participants that had taken no drugs in the previous 30 days were given one of 3 doses (n=12 per dose) of OxyContin®. The following shows the combined distribution of multiple urine specimens taken from each individual days 3 and 4 after dosing began:



Interpretation Cautions

- Interferents, sensitivity and cutoffs vary by immunoassay, see Reference 3 for a review of immunoassay types and interferents; EMIT assays are used by Regions Hospital's Toxicology lab, which serves the entire HP Family of Care.
- Hydromorphone has been shown to be a minor metabolite in chronic pain patients receiving high amounts of morphine.[4,5]
- Hydrocodone has been shown to be a minor metabolite detectable in patients on high amounts of codeine[6]; as the metabolite of hydrocodone, hydromorphone may also be detectable in these cases.
- A small amount of codeine may be evident with morphine administration due to manufacturing impurities (up to 0.04% of parent dose); high amounts of morphine should be present in these cases.[7]
- A small amount of hydrocodone may be evident with oxycodone administration due to manufacturing impurities; high amounts of oxycodone should be present in these cases[8]
- Ingestion of poppy seeds or herbal teas containing Papaveris fructus may cause a true positive opiate (morphine, codeine) results.[9,10]
- Oxymorphone has a longer half-life than oxycodone; a patient prescribed oxycodone may only have oxymorphone detected in urine.
- Heroin is metabolized to morphine, which may be detectable after its use.
- The dose taken cannot be extrapolated from drug screen results, even if a quantitative result is obtained.

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Questions: Please reply to this e-mail, and your questions(s) will be directed to the author of this Pearl, Kalen Olson, PhD, Clinical Laboratory Director.