

FOCUS ON URINE DRUG MONITORING

Are your patients compliant, diverting, or supplementing the drugs that are prescribed for their chronic pain?

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[Editor's note: It is increasingly clear that patients receiving Schedule II pain medications should be monitored for compliance, diversion, and supplementation—whether by blood or urine testing. This article describes a urine-monitoring program developed by Ameritox, Ltd (RxGuardianSM) that identifies the drugs and/or metabolites in the patient's urine along with expected ranges of compliance.]

“Chronic pain is a significant problem in the U.S. today. 35% of patients have chronic pain. Over 50 million Americans are partially or totally disabled by chronic pain. Over the age of 50, one out of two people suffer from chronic pain. Under-treatment of chronic pain runs as high as 50%. With the reversing of the aging of the population this number will be increasing rapidly over the next several decades. The effects of under-treatment of pain can be devastating, including, for example, depression (suicidal ideation), anxiety, loss of sleep, social and sexual dysfunction, loss of work, weakness, fatigue, gastrointestinal distress, hypertension and tachycardia.”¹ The JCAHO has made pain management one of its number one issues for accreditation for hospitals, and now pain is recognized as the fifth vital sign.²

In their October 23, 2001 Consensus Statement,³ the DEA and 21 healthcare organizations agreed that “effective pain management is an integral and important aspect of the quality of medical care and pain should be treated aggressively.” They also noted that opioids are often “the most effective way to treat pain and the only treatment option to provide significant relief.” They further stated “that focusing only on the abuse potential of the drugs,

however, could erroneously lead to the conclusion that these medications should be avoided when medically indicated, generating a sense of fear rather than respect for the legitimate properties.”

In the late 1980s and early 1990s, a major breakthrough in the management of non-malignant pain was the use of opioids. Opioids are the most effective known analgesics. On May 19, 1998, the Federation of State Medical Boards published the Model Guidelines for the Use of Controlled Substances for the Treatment of Pain (revised in 2004).⁴ These Guidelines recognize that “controlled substances” including opioid analgesics may be essential in the treatment of acute pain due to trauma or surgery and in chronic pain whether due to cancer or non-cancer origins.

Benefits of Drug Testing

The use of a drug-testing program for all patients receiving opioid therapy is essential. Testing patients can reveal other comorbidities, depression, addiction and poor adherence or compliance. If managed appropriately, patients receive excellent pain relief and, in many cases, are able to achieve improved functionality. Some are able to return to work and even those who do not achieve this goal, may still improve their overall quality of life. A well-designed drug-testing program will allow the physician to determine whether the patient is using illegal drugs or using additional prescription drugs (multiple prescribers). Patients tend to under-report illicit drug use. The abuse of other drugs also increases the risk of adverse drug reactions, overdose, and treatment failure.

So, after all is said and done, what can the physician hope to gain by subjecting the patient to a drug-testing program?

1. Drug testing can help provide answers to the following questions:
 - Is the patient taking only the specific drugs prescribed?
 - Is the patient taking other drugs that in combination could be harmful?
 - Is the patient not taking the prescribed drugs?
2. The urine drug test serves as documentation that the physician is evaluating the prescribing of drugs to his patient.
3. The test program provides information which can help the physician provide better patient care, help identify drug seekers and patients with possible addiction issues.

Establishing A Drug Testing Program

Since there are many different types of programs which can be utilized, it becomes imperative that the physician adopt a program that tests appropriately and specifically for the drugs the physician prescribes. The program should possess the sensitivity to detect those drugs and/or their metabolites at the concentrations that would be consistent with expectations based on the physician's prescribing dose for the patient. The monitoring program must also address the matrix to test. If the goal is to actually measure the amount of a drug in a patient after he or she achieves a "steady state" concentration, then the tests should be done on plasma or serum. However, if the goal is multi-purpose and includes the need to establish that the patient is not taking a broad base of different drugs and that the patient is taking what is prescribed, then urine may be the best suited specimen to utilize. Urine has been the most extensively studied matrix for testing programs. It will provide not only acute history but also a retrospective look at drug activity for a number of days. Once it has been decided which matrix to test, the next step is to determine which drugs should be included in the testing program.

Urine Drug Testing

Urine drug testing programs generally include various "panels" to choose from. If the focus is on pain management drugs, particularly the opioids, then one needs

DRUG/METABOLITES	SCREENING CUTOFF (NG/ML)	CONFIRMATION CUTOFF (NG/ML)	DRUG/METABOLITES	SCREENING CUTOFF (NG/ML)	CONFIRMATION CUTOFF (NG/ML)
Amphetamines	1000		Lorazepam		75
Amphetamine		125	Nordiazepam		75
Methamphetamine		125	Oxazepam		75
Cannabinoids	30		Methadone	150	
THCA		4	Methadone		100
			EDDP		100
Cocaine	200		Propoxyphene	200	
Benzoylcegonine		10	Propoxyphene		100
			Norpropoxyphene		100
Opioids	50		Add On Tests		
Codeine		100	Alcohol	20mg/dl	20mg/dl
Hydrocodone		100			
Hydromorphone		100	Fentanyl	NA	
Morphine		100	Fentanyl		3
Oxycodone	*	*	Norfentanyl		10
Oxymorphone	*	*			
PCP	25	25	Meperidine	NA	
			Meperidine		1000
			Normeperidine		
Barbiturates	200		Carisoprodol		
Secobarbital		100	Meprobamate		
Butalbital		100	Buprenorphine	5	NA
Pentobarbital		100			
Phenobarbital		100	MDMA(Ecstasy)	500	
*Oxycodone	100		MDMA		100
Oxycodone		100	MDA		100
Oxymorphone		100	MDEA		100
Benzodiazepines	100		Gabapentin	NA	5000
Alprazolam		75			
á-OH-Alprazolam		75			

TABLE 1. Sample Urine Drug Panel with add on tests. (Courtesy of Ameritox, Inc.)

to choose a panel that will cover those drugs. A sample pain management panel is shown in Table 1 and includes optional add on tests.

In most laboratories, the testing begins with immunoassays which are based on competitive reactions between the drug of interest and a "labeled" drug added to the specimen for sites on an antibody for the drug of interest. Two common immunoassay tests are described below along with a description of the terms cutoff, sensitivity and specificity.

Enzyme Immunoassay (EIA)

In enzyme immunoassay (EIA), the label on the antigen (drug) is an enzyme. The specimen (urine) to be tested is mixed with the reagent containing a substrate for the enzyme and antibodies to the drug of

interest. A second reagent containing the enzyme labeled drug is added to the specimen. The enzyme becomes inactive when bound to an antibody site. The more a drug of interest or its metabolites that is present in the specimen, the more enzyme activity that will be measured. This increase in enzyme activity is seen because the presence of the drug or its metabolite in the specimen ties up the limited number of antibody sites. The measured reaction is directly proportional to the amount of drug of interest and/or its metabolites in the specimen.

Fluorescent Polarization Immunoassay (FPIA)

In fluorescent polarization immunoassay (FPIA), the "label" on the antigen (drug) is a fluorescent substance. The labeled

Laboratories	Cutoffs Opioids (ng/ml)	Presumptive Positives	% Difference
Ameritox	50	176	—
Others	300	161	8.5
DOT	2000	77	56.2

TABLE 2. 245 specimens tested by Immunoassay (EIA) using different cutoffs.

drug and the drug of interest and or its metabolites compete for the limited sites on the antibodies. When a fluorophore is excited with polarized light, it gives off polarized light. A larger molecule will emit a greater proportion of polarized light. If the labeled drug combines with the antibody site it has the effect of creating a larger molecule and therefore more fluorescence. The FPIA test is known to give a better quantitative response for the class of drug of interest than EIA. The measured reaction is indirectly proportional to the drug of interest and or its metabolites in the specimen.

Cutoff Level

The immunoassay cutoff level is the urine concentration level at which a sample is labeled as “positive” or “negative” for a drug. Cutoff levels have been identified for use in occupational testing as determined by the Substance Abuse and Mental Health Services Administration (SAMHSA) or as set by State statute. A urine sample that is at or above the cutoff level is labeled as “positive/detected” or, if below the cutoff level, as “negative/none detected” for the drug(s) tested. For drug testing in pain management, it is desirable to have much lower cutoffs for most of these classes of drugs. For example, opioids should be subject to a cutoff level of 50 ng/ml versus the industry standard of 300 ng/ml. Note that normal employee drug tests (DOT) testing utilizes a cutoff of 2000 ng/ml. Furthermore, it is desirable to utilize normalized relative quantitative values instead of just a qualitative “positive” or “negative” result. If the immunoassay value of the urine sample is equal to or greater than the “cutoff level,” the sample is submitted for confirmation by Gas Chromatography/Mass Spectrometry (GC/MS).

Sensitivity

Any successful testing hinges on how sensitive the test is to the drugs that are present. It is important that the tests used have adequate sensitivity for the drugs being

tested for; otherwise a drug may be present and go undetected. The lower the cutoff level, the more sensitive the test.

Specificity

Testing should only give a positive result for the drugs of interest and not be affected by other drugs or chemicals. EIA and FPIA are very specific for each of the drug classes tested, however, there are some chemicals or drugs that may interfere with the test and give a positive test result when, in fact, the drugs being tested for are not there. GC/MS is 100% specific. GC/MS uses a “fingerprinting” of each of the drugs and metabolites, and there are no drugs or chemicals which will give a positive test result except for the ones being tested. This is why the GC/MS technique is considered the “gold standard” of confirmation testing. In the initial immunoassay test, the specificity of the test decreases as cutoff levels are lowered.

The Testing Process

The testing process begins with an initial test, sometimes referred to as a screening test. This initial/screening test is an immunoassay. An immunoassay is used to indicate whether a patient may have used a class of drugs—opiates, for example. A “cutoff” is used on all immunoassays and this is the response used to indicate whether the sample is “presumptive positive.” A result which is equal to or above the cutoff for the sample is considered presumptive positive. A result below the cutoff the sample is considered negative for that drug class. The rule is: the lower the cutoff, the more sensitive the assay. This means by lowering the cutoff, the patient has a greater chance to be consistent with what was prescribed. However lowering the cutoff level increases the chances that non-prescribed drugs will also be detected.

The sample drug test panel, described in Table 1, offers a very comprehensive opioid panel including codeine, morphine, hydrocodone, hydromorphone, oxycodone and oxymorphone, with op-

tions for adding meperidine, fentanyl, propoxyphene, tramadol at very low cutoffs. This panel performs initial opioids tests at a 50 ng/ml cutoff using enzyme immunoassays (EIA) followed by a second immunoassay for all positives using fluorescence polarization immunoassay (FPIA), an equally sensitive and more quantitative test. All specimens are also tested using a third enzyme immunoassay developed specifically for oxycodone.¹

The Oxycodone immunoassay kit has been shown to provide a highly reliable method for the detection of oxycodone and/or oxymorphone in urine specimens.² Any response greater than 50 ng/ml (100 ng for the oxycodone immunoassay) is subjected to a confirmation test by Gas Chromatography/Mass Spectrometry (GC/MS). GC/MS is capable of identifying a drug at the molecular level and therefore provides a “fingerprint” identification. It can also be used to give a quantification of the amount of a specific drug and/or its metabolite present in the urine and is usually reported in nanograms per milliliter of urine.

The illustrated 50 ng/ml cutoff for the initial opiate test is 40 times more challenging than normal employee drug tests (DOT) which use a 2000 ng/ml screen and 6 times more sensitive than the current industry standard of 300 ng/ml opiate screen cutoff. Table 2 presents the results of 245 specimens tested using a cutoff of 50 ng/ml versus the DOT and current industry standard for the opiates. This more stringent cutoff detected 15 more presumptive positive opiates than the 300 cutoff procedure and 99 more than the DOT cutoff, which equates to 8.5 % and 56.2% more, respectively. Any samples identified as “presumptive positive” are then tested with gas chromatography/mass spectrometry (GC/MS) for positive identification. The GC/MS cutoff for confirmation is 100 ng/ml for each of the individual opiate drugs (hydrocodone, hydromorphone, codeine, morphine, oxycodone and oxymorphone), which is 3 times as sensitive as the current industry standard of 300 ng/ml cutoff.

This illustration makes it clear that unless a very sensitive immunoassay cutoff is utilized, a patient on “low dose therapy” stands a considerable chance of screening negative. Furthermore, if the patient’s specimen does screen as a “presumptive positive,” the specimen may appear to confirm negative by GC/MS unless the opi-

ate confirmation cutoffs for this latter test are also set at very low concentrations (typically 100 ng/ml versus the current industry standard of 300 ng/ml).

Interpretation

In order to understand the results of a urine drug test, the physician must have an understanding of the metabolism of the drugs prescribed in order to be able to clearly interpret the findings. This is complicated because the metabolites of many of the commonly prescribed opiates are also commonly prescribed parent opiate drugs (see Table 3).

A proprietary tool used to compare a patient's test results to an expected range is the RxGuardianSM Report (by Ameritox Ltd). Based on a patented algorithm which produces an estimate based on the FPIA class reactivity to determine compliance, the algorithm used in this report calculates a normalized FPIA value using the patient's height and weight, the specimen's pH and specific gravity. An FPIA range is then developed from the prescription dosage information enabling a comparison of the normalized value to the expected range. The comparison between the normalized FPIA result and the developed range provides a measure of compliance with the prescribed dose. If the normalized FPIA value falls in range, the FPIA Interpretation will be reported "IN RANGE," if the patient's normalized value falls below the range than the patient is considered "NORMLO" and if the patient's normalized value falls outside the predicted range on the high side the patient is "NORMHI." While the aforementioned algorithm estimates the plasma concentration of methadone, all other drugs are evaluated based on whether the normalized FPIA result is consistent with the patient information provided and the laboratory's measured values. If the normalized value falls in the expected range then the patient is considered compliant. The RxGuardianSM process also reports whether the findings are consistent or inconsistent with the prescribed medications.

Discussion And Conclusion

The urine-testing program described above offers a measure of compliance (expected values based on patient and initial laboratory results) and an indication of whether the molecular identifications of the drugs determined by GC/MS are con-

Drug Class	DRUG	DRUG AND / OR METABOLITE
Amphetamine	Amphetamine	Amphetamine
	Methamphetamine	Amphetamine, Methamphetamine
Barbiturates	Butalbital	Butalbital
	Pentobarbital	Pentobarbital
	Secobarbital	Secobarbital
	Phenobarbital	Secobarbital
Benzodiazepines	Alprazolam	Alprazolam Álphahydroxyalprazolam
	Diazepam	Oxazepam, Nordiazepam
	Lorazepam	Lorazepam
	Nordiazepam	Nordiazepam, Oxazepam
	Oxazepam	Oxazepam
	Temazepam	Oxazepam
Cannabinoids	THCA	THCA
Cocaine	Cocaine	Benzoylcegonine
Methadone	Methadone	Methadone, EDDP
Opioids	Codeine	Codeine, Morphine
	Hydrocodone	Hydrocodone, Hydromorphone
	Hydromorphone	Hydromorphone
	Morphine	Morphine
	Oxycodone	Oxycodone, Oxymorphone
	Oxymorphone	Oxymorphone
Phencyclidine	PCP	PCP
Propoxyphene	Propoxyphene	Propoxyphene, Norpropoxyphene
Add-On-Testing		
Carisoprodol	Carisoprodol	Meprobamate
Meprobamate	Meprobamate	Meprobamate
Fentanyl	Fentanyl	Fentanyl, Norfentanyl
Meperidine	Meperidine	Meperidine, Normeperidine
Tramadol	Tramadol	Tramadol
Buprenorphine	Buprenorphine	Buprenorphine
Nicotine	Nicotine	Cotinine
Gabapentin	Gabapentin	Gabapentin

TABLE 3. *Understanding Metabolism*

sistent or inconsistent with the prescribed medications. There have also been many reported cases alleging malpractice or wrongful death related to suicide attempts. Testing patients is an important element in demonstrating that a physician is making a conscientious attempt to monitor pain patients. Monitoring allows one to treat patients better, detect possible addiction or diversion, and meet local

and federal government requirements concerning the prescribing of opioids.

It must be noted that, by utilizing very sensitive cutoffs, some specimens may test positive due to drugs present in food products or over-the-counter-medications. The most common problem is that of morphine found in poppy seeds. The eating of one poppy seed bagel has resulted in as much as 800 ng/ml of morphine

for up to eight hours. Amphetamine-like drugs in over-the-counter medications, including pseudoephedrine and ephedrine, give a positive initial test if present in high enough concentrations, but will not confirm by GC/MS. When results are inconsistent with what is expected, communication with a toxicologist at the laboratory is critical. Toxicology specialists can assist the physician in understanding the reports and help explain any unanticipated results. Finally, it is usually best to test patients on a regular basis to measure compliance and detect any changes in a patients' drug taking behavior.

However, it must be remembered that no drug testing program can take into account all factors that may influence the test result. For example, metabolism may be altered by other drugs a patient is taking. Different individuals may metabolize at different rates depending on genetic factors or physical conditions, including liver and kidney disease, diabetes, and even pregnancy. It is also well known that immunoassays can cross-react with drugs similar to those the assay is targeted for. This may trigger "false positives" or, because of low cross-reactivity of some drugs of interest, may result in "false negatives." Therefore, whenever the results are inconsistent, consulting a toxicology specialist and/or referring the patient to an addictionologist should be considered. ■

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