How Can a Methadone and an Opiate-Positive Immunoassay Result be Reconciled in a Patient Prescribed only OxyContin and Wellbutrin?

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Abstract. Appropriate management of patients in pain clinics can be complex and sometimes confusing because providers must correctly interpret multiple sources of patient information. The correct interpretation of laboratory results is essential to guide subsequent patient treatment and management; however, laboratory and clinical pictures can appear to be conflicting in cases of substance abuse. Incorrect interpretation of laboratory results can multiply negative impacts on clinical outcomes and may lead to patient harm or death.

This report introduces the complex nature involved in understanding and interpreting urine drug testing (UDT) results in pain patients who are prescribed opioid medications. Laboratory testing examples of UDT results are provided to illustrate the sometimes discordant nature of UDT interpretation. This case study describes one method of approaching cases where laboratory result interpretation in pain clinic patients is essential for medical treatment and management. The case presented in this manuscript illustrates a reconciliation of an opiate positive immunoassay result in a patient who was prescribed only OxyContin and Wellbutrin after traumatic amputations.

Key words: Urine Drug Testing, Pain management, methadone, oxycodone

Introduction

Various clinically available urine drug tests (UDTs) may produce results that can initially appear to be conflicting with the patient presentation, history, and/or prescription use. Interpretation of aberrant UDT results may be incorrect due to a lack of traditional training or education in the field of pain management for the treatment of addiction disorders [1,2]. Understanding and correctly interpreting UDT results are critical components in managing patient care in terms of compliance, aberrant behavior, diagnosis of drug addiction or diversion, and development of subsequent treatments strategies. While this might appear to be an easy task apparently solvable via an algorithm, difficulties related to UDT interpretation are underscored by the following quote published almost 30 years ago by Burglass and Shaffer [3]: “Certain individuals use certain substances in certain ways thought at certain times to be unacceptable by certain other individuals for reasons both certain and uncertain.”

In maximizing UDT results for managing pain patients, primary care providers must have a strong ability to interpret results in conjunction with an understanding of metabolites, laboratory cut-off values, and testing frequency. For example, it is important to know that a patient taking codeine may have a positive UDT for codeine, morphine, hydrocodone, and hydromorphone. However, if morphine is the only negative result in that patient, then the interpretation could be explained in terms of a concomitant medication such as bupropion, which could function as a P450 2D6 inhibitor that
prevents the conversion of codeine to morphine. In some instances, the drug being prescribed may be better known as a metabolite. For example, parent drugs such as morphine and oxycodone should not be detected if the prescribed drugs are hydromorphone or oxymorphone, respectively. With respect to benzodiazepine metabolism, positive oxazepam and temazepam results in a patient taking prescribed diazepam should be expected. While expected UDT results can be interpreted in the context of prescribed drugs, unexpected UDTs may be caused by a combination of pharmacogenetic variability, false positive or negatives results, impurities, and/or aberrant behavior.

Currently, safe and clinically appropriate opioid prescribing requires a thorough understanding of both pain management and laboratory testing. Increasing the understanding of these two areas will improve patient management in terms of diminishing overdose risk, drug abuse, addictive or aberrant behavior, and diversion. While there is a lack of consensus among pain specialists about patient testing paradigms, there is strong agreement that UDTs should be used for clinical assessments and drug prescribing for pain patients [4,5]. Pain management experts also agree with laboratory medicine specialists that UDTs, like any laboratory test, can be completely meaningless unless a correct understanding and interpretation of results is appreciated in the context of each clinical case [6,7]. The following case illustrates several key points about UDTs in the context of safe opioid prescribing and interpretation of laboratory results.

**Case Description**

A 26-year-old male submitted to a urine drug test (UDT) during a scheduled visit with his primary care provider. 18-months prior to this visit, he stepped onto an Improvised Explosive Device (IED) during a military deployment mission and sustained a traumatic amputation of the leg directly above the knee, soft tissue injury in the region between L-2 and L-4, and loss of his hand. During the first 16 months of treatment and rehabilitation, the patient made significant progress in physical and psychological recovery and was taken off of all prescription medication at month 16 except for bupropion (Wellbutrin®).

Despite a strong initial recovery, during the past two months the patient experienced a decline in social interactions, became withdrawn, exhibited signs of increasing anxiety, and complained about increasing lower back pain recently reinjured from falling down a flight of stairs. The patient was prescribed OxyContin after the fall (month 17). Family history for anxiety and depression was documented for his father and paternal grandmother. The provider ordered UDTs because he was concerned about recent emerging aberrant behavior and inconsistent patient statements. Upon further questioning, the patient admitted to “maybe borrowing methadone from a friend.” The hospital
UDT screen report indicated a positive immunoassay result for opiates and was negative for amphetamines, tetrahydrocannabinol (THC), and cocaine. A methadone test was separately requested because of the patient’s admission of possible use. Subsequently, the sample was sent to a reference lab for the confirmation of opiates (codeine, hydrocodone, hydromorphone, and morphine) and to investigate methadone abuse. GC/MS testing confirmed the presence of oxycodone, oxymorphone, hydromorphone, and hydrocodone. Additional confirmation testing from the reference laboratory detected both methadone and the methadone metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).

Because the patient initially stated that he had taken only the prescribed oxycodone for pain and Wellbutrin® before admitting to “borrowing methadone,” the provider expressed concern about possible immunoassay interferences or the possibility of additional drugs that the patient may have taken but not disclosed. These concerns prompted the provider to ask the laboratory director for further guidance on the laboratory evaluation of this patient.

**Case Discussion**

There are some related groups of questions to be cognizant of when considering the key elements in this case. The overall goal is to determine how to maximize patient care and pain management by narrowing the information gaps between the provider and the laboratory. With respect to the laboratory testing in this case, questions will likely be related to identifying different classes of drugs. For example, when ordering testing, it may be useful to know if the lab offers separate immunoassays for both methadone and opiates. With respect to the clinical components of this case, questions to answer may be related to different presentations of true or false positive opiate screens, and how specific clinical presentations should guide UDT testing and interpretation.

Important laboratory testing concepts relates chemical structures of drugs to immunoassay detection. For example, methadone’s core structure significantly differs from morphine, codeine, or oxycodone (Figure 1). Therefore, it is unlikely that those other drug structures will interfere with methadone specific screening immunoassays. However, in this case it may be important to consider that opiate immunoassays can be specific for morphine and demonstrate varying cross-reactivity levels for codeine, hydrocodone, and hydromorphone [8] and poor cross-reactivity for oxycodone or oxymorphone [9]. In order to guide appropriate testing in other cases, providers should know that most opiate screens fail to detect synthetic opioids such as fentanyl or meperidine.

In the case presented here, GC/MS confirmation did not detect methadone because methadone was not part of the requested opiate screen. Oxycodone is metabolized by both CYP3A4 and 3A5 to noroxycodone and by CYP2D6 to oxymorphone [10], which explains the oxymorphone confirmation. However, an additional drug is indicated because hydromorphone is a metabolite of hydrocodone and cannot come from oxycodone (Figure 2).
Unexpected screening result in a patient prescribed oxycodone

Patients who are compliant with methadone treatment excrete urine containing both the parent drug and EDDP [11], explaining the presence of EDDP reported by the reference laboratory. An EDDP/Methadone ratio greater than 0.60 is consistent with compliance for patients who are prescribed methadone; the ratio is generally less than 0.10 in urine samples that are spiked with methadone by patients who may be diverting their prescription [12]. In this case, in addition to the other drugs detected, methadone use was confirmed by subsequent clinical follow-up due to initial detection of methadone by the screening assay and metabolite of the parent drug in the confirmation testing.

UDT detection of a drug is a function of parent drug and metabolite structures in conjunction with urine concentrations and cut-off values. For example, opiate immunoassays screens are sensitive to morphine and codeine but may not indicate which one is present. Because of varying cross-reactivity among immunoassays, lower sensitivity is demonstrated for semisynthetic and synthetic opioids, even at significantly high concentrations [13]. Therefore, negative results should be interpreted with caution and considered in conjunction with the clinical picture. Structurally unrelated compounds can produce false positive results in some opioid immunoassays. This has been demonstrated in the cross reactions of quinolone antibiotics (e.g., levofloxacin, ofloxacin) and the antidepressant trazodone with fentanyl. In such cases, GC/MS or LC/MS/MS confirmation testing will confirm and clarify questionable UDT results.

Detection times for opiates and many opioids range from 1-3 days [7]. Because positive results do not provide definitive information on dose, drug exposure intervals, time of last dose, or source, UDT results should not be used in attempts to calculate or make assumptions about drug doses consumed. Unexpected true positive results in a clinical setting, as in this case, require further assessment to determine a follow-up strategy for possible medical intervention and management. In this case, the identification of a substance abuse disorder does not marginalize the patient’s complaint of back pain; however, it does make the medical management more difficult.

True positive UDT results can come from medications prescribed by different providers, use of over the counter/internet medications, or some dietary foods or supplements. Thorough documentation and patient discussion often facilitates accurate interpretation between true and false positives results. For example, while the presence of morphine and 6-monoacetylmorphine in urine from patients not prescribed morphine indicates heroin use, codeine or poppy seed consumption may also produce a true positive morphine result (Figure 1).

Because codeine is metabolized to morphine, both drugs may be detected in urine following codeine use. Therefore, while a codeine prescription may explain positive codeine and morphine results, it may not always explain the presence of morphine only, and it may suggest heroin or morphine use. Additionally, a positive codeine result could not be explained by a morphine prescription because metabolism from codeine to morphine is unidirectional. In similar cases, the detection of only codeine may be possible in Caucasians because about 10% lack CYP2D6 activity and therefore lack the ability to convert codeine to morphine [14]. While morphine and hydrocodone each can be metabolized to produce small detectable amounts of hydromorphone, codeine metabolism may not produce detectable amounts of hydromorphone on screening [6]. Therefore, hydrocodone in urine that also contains codeine should not be considered as evidence of hydrocodone use and may be a function of dose timing rather than co-administration of a second drug.

As previously stated, studies have reported that lack of provider training on UDT interpretation has been problematic. One study reported that only 12% of primary care physicians knew that testing for oxycodone must be specifically requested when ordering a UDT [1]. In another study, only 23% of providers stated they would consult the laboratory when confronted with an unexpected UDT that they could not explain [2]. Such
disconnects underscore the importance of provider and laboratory communication to understand relationships between laboratory policies and UDT results in pain management cases. The importance for continued education is more evident when considering data from the National Survey on Drug Use and Health stating that about 33% of people > 12 years old using drugs for the first time in 2009 started non-medical use of prescription drugs, and that more than 70% of people using prescription pain relievers obtained them from friends or relatives.

Summary and Conclusions

In this case there are several noteworthy points to remember: First, UDT results must be correctly understood in the context of the clinical presentation because they are critical in managing patient care in terms of compliance, diagnosis of drug addiction or diversion, and to develop subsequent treatment strategies. Next, safe and clinically appropriate opiate prescribing requires a thorough understanding of both pain management and laboratory testing. Also, opiate immunoassays are specific for morphine with varying cross-reactivity levels for codeine, hydrocodone, and hydromorphone, demonstrate poor cross-reactivity for oxycodone or oxymorphone, and may fail to detect synthetic opiates such as fentanyl. Last, unexpected true positive UDT results likely indicate a substance-abuse disorder that will require medical intervention and management to prevent patient harm.

Because the provider continued to question the patient about emerging aberrant behavior, additional UDTs for methadone was ordered. Without persistent follow-up and discussions with the laboratory, the provider may not have determined the true cause for the UDT results, and this case may have ended in patient harm.

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References