Clinical Update: August 2021

Cases of Unusual Buprenorphine Concentrations in Urine Drug Tests: What Does This Mean and What are the Clinical Implications?

Buprenorphine is a semisynthetic opioid with partial agonist activity at the mu-opioid receptor, an effective treatment option for opioid use disorder (OUD) due to its ability to suppress opioid withdrawal and block exogenous opioid effects. The Center for Disease Control and Prevention estimates there are 91 deaths in the United States each day due to opioids.[1] Patients with OUD often seek treatment from providers who may offer buprenorphine therapy as part of medication-assisted treatment (MAT). Urine drug testing is one way a provider can assess compliance to a prescribed buprenorphine regimen, a practice that clinical guidelines and professional pain organizations recommend.[2] High complexity labs, such as Aegis, are capable of quantitatively detecting both the parent buprenorphine and metabolites via definitive testing of patient specimens. When evaluating the quantitative results for buprenorphine identified in a urine specimen, the ratio of the parent drug to metabolite can give a provider insight into medication compliance or possible sample adulteration (i.e. drug addition or "shaving"). In this month's Clinical Update, we discuss two example reports of possible buprenorphine adulteration and the clinical implications of potential opioid overdose or diversion.

Aegis employs a definitive testing method (liquid chromatography/tandem mass spectrometry) in all reporting of positive test results. For analysis of buprenorphine, both parent drug (buprenorphine) and metabolite (norbuprenorphine) are quantitatively determined, and for urine specimens, the ratio of parent drug to metabolite is analyzed. When parent buprenorphine far exceeds norbuprenorphine, such as ratios 35-50 times greater, sample adulteration is suspected.[3] An example of a real-life sample where adulteration is possible is shown below in Figure 1. Parent buprenorphine is above the upper limit of quantification (>5000 ng/ml) and the ratio of parent buprenorphine: norbuprenorphine is >277. Low norbuprenorphine concentrations have been reported when patients have admitted to submerging their medication directly into the urine cup immediately after collection.[4] Conversion of parent drug to metabolite may occur because of drug degradation due to the physiologic temperature of urine.

Figure 1: High Parent Buprenorphine

Clinic Information	Patient Information	Sample Information	
Client:	**Patient Name:**	**Lab Sample ID:**	
		Specimen Type:	Urine
	Patient ID:	**Collected:**	4/2/2021
Requesting Provider:	**Date of Birth:**	**Received:**	4/3/2021
	Male/Female:	**Reported:**	4/6/2021

Medication(s) Prescribed

None Indicated

Test(s) Requested

00199U - PainComp QMP 199	04160 - Designer Opioids	04110 - Synthetic Stimulants
04420 - Barbiturates	04440 - Marijuana	
04120 - Designer Benzodiazepines	04140 - Synthetic Cannabinoids	

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Buprenorphine	See comment	>5010 ng/mL	Low metabolite concentration suggests possible adulteration. For additional information, please consult clinical scientists at 1-877-552-3232.

BioDetect™

Result	Comment
EXPECTED	Test result is consistent with routinely analyzed human urine.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Buprenorphine		
Buprenorphine	**POSITIVE**	>5000 ng/mL
Norbuprenorphine	**POSITIVE**	18 ng/mL

In March 2021 Aegis launched a next generation urine specimen validity test called BioDetect™, which detects several different compounds routinely found in human urine.[5] When all components of the BioDetect test are absent from the submitted urine specimen, the sample report receives a "Not Expected" BioDetect result. When this occurs, it is possible that the urine specimen was substituted at the point of collection with something such as synthetic urine or other non-urine substances, and this should be evaluated by the ordering provider. An example report demonstrating a specimen that appears to have been substituted based on the BioDetect results with possible buprenorphine adulteration is shown in Figure 2. Parent buprenorphine is also above the upper limit of quantification and the ratio of parent buprenorphine: norbuprenorphine is >277. Although not shown, this sample had normal urine creatinine and pH, consistent with a synthetic urine kit.[6]

Figure 2: BioDetect™ Unexpected

BioDetect™

Result	Comment
Not Expected	Please contact the Clinical Team at 1-877-552-3232 for more information.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Buprenorphine		
Buprenorphine	**POSITIVE**	>5000 ng/mL
Norbuprenorphine	**POSITIVE**	18 ng/mL
Bupropion	NONE DETECTED	
Antipsychotics	NONE DETECTED	
Amphetamines	NONE DETECTED	
Benzodiazepines	NONE DETECTED	
Cannabinoids (Marijuana)	NONE DETECTED	
Gabapentin/Pregabalin	NONE DETECTED	
Cocaine Metabolite	NONE DETECTED	
Opiates	NONE DETECTED	

When reviewing a sample result that indicates adulteration or specimen substitution, providers may question what drove the patient's aberrant behaviors. If the medication is clearly being added to the specimen, is it being taken at all by the patient? If the specimen is substituted, what was the patient potentially using that was unable to be detected? Is there actual risk for diversion of buprenorphine products, and are individuals with a history of OUD at increased risk for adverse outcomes when they divert medication?

The answers to these questions may be difficult to obtain, but certainly something to consider. A clinical consideration for providers who may experience one of these two scenarios is a potential increased risk of overdose. Although risk of overdose is significantly decreased in MAT programs, patients often cycle in and out of treatment. During this time, some patients may adulterate their samples with buprenorphine to appear compliant while still using illicit drugs.[7] A study by Krawczyk et al. found opioid overdose death was significantly lower during medication treatment periods compared to non-medication treatment in specialty care settings (HR= 0.18).[8] Demographics differed between the two groups, where patients who were not in MAT were more likely to be male, single, unemployed, homeless, had sought mental health treatment, or reported arrest with subsequent criminal justice referral.[9] These characteristics may be helpful to clinicians in identifying individuals who may be at higher risk of opioid overdose. Another study evaluated mortality in patients engaged in buprenorphine treatment found that the greatest risk for overdose were in those who were male, homeless, or had history of hepatitis C infection. Additionally, the risk of a fatal overdose was up to five times greater for individuals who have previously experienced a non-fatal opioid overdose.[10] Those patients with a repeat overdose are more

likely to continue to receive high-dose prescription opioids along with using other substances. Thirty-six percent of opioid-related deaths also involved a stimulant (i.e., cocaine or amphetamines) and 47% involved other substances such as cannabis, benzodiazepines, gabapentin, and alcohol. Identifying these high-risk patients is important to help guide patient-specific therapy and education to help improve outcomes.

Studies assessing risk for buprenorphine diversion often involve surveys where individuals who are part of OUD treatment are asked about abuse or misuse. Data from >10,000 subjects from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System showed about 33% of survey respondents had misused buprenorphine in the past month.[11] However, these studies asked only about drugs misused in the past month, so the question may have biased the responses provided by participants. In addition, participants indicated that buprenorphine was primarily not their drug of choice, and many (63%) stated they were using illicit buprenorphine for issues related to opioid withdrawal.[12] Thus, the illicit buprenorphine market and diversion of legitimately prescribed buprenorphine may be partly driven by individuals who are not in formal OUD or MAT programs. Potential reasons individuals may choose to self-treat their addiction to opioids with buprenorphine includes insufficient access to prescribed buprenorphine, cost of care, stigma associated with addiction and illegal drug use, or lack of access to opioids of choice when withdrawal symptoms begin.[11]

Studies reporting reasons for buprenorphine diversion are generally small in sample size but tend to report similar trends of behavior. These reasons include helping a friend or someone in their social network with withdrawal, to sell because they need money, or to get high.[14] Patients already enrolled in a buprenorphine-based MAT program may also obtain non-prescribed buprenorphine in addition to what they are prescribed because of a need for additional treatment, or possibly also for diversion purposes as mentioned above.[14] The reasons a patient may divert buprenorphine treatment probably vary throughout time during the course of their addiction. When routine medication monitoring results such as through routine urine drug testing shows unexpected results, providers should be aware of possible reasons for such behaviors. This insight may help providers to better understand their patient's motivation, attempt to minimize the behavior, without affecting the provider-patient relationship.

NOTICE: The information above is intended as a resource for healthcare providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

References:

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