Clinical Update: March 2022

WHAT DID MY PATIENT ACTUALLY TAKE? CODEINE RESULTS INTERPRETATION

Codeine is an all-natural opioid that is found in opium and is used pharmaceutically to treat mild to moderately severe pain. The interpretation of codeine and other drugs in drug testing can be complicated due to the many variables that can affect the presence of metabolites. Codeine can be metabolized to norcodeine, morphine, hydrocodone, norhydrocodone, hydromorphone, and dihydrocodeine. Furthermore, the metabolites morphine, hydrocodone, and hydromorphone are also drugs that can be prescribed (Figure 1).[1] Please note that the interpretation of results differs when using presumptive vs. definitive testing methods and may also differ among laboratories. The information provided here is intended to assist providers with deciphering positive codeine results reported by Aegis, which have undergone definitive testing by liquid chromatography/tandem mass spectrometry.

Codeine Metabolism

Norcodeine, the normetabolite of codeine, is a unique biomarker that results from the CYP 3A4 metabolism of codeine after ingestion.[2] Although norcodeine possesses weak opioid activity, it is not likely to contribute to the overall analgesic effect.[3-5] CYP3A4 metabolism is subject to induction and inhibition by many drug-drug and drug-food interactions, potentially altering opioid normetabolite concentrations.[6-10] Drugs that inhibit or induce the CYP3A4 route of metabolism can modify the effect of opioids by increasing or decreasing analgesic effects or causing adverse drug effects such as sedation, respiratory depression, and/or death.

Morphine, hydrocodone, and hydromorphone are pharmacologically active metabolites of codeine and are products of CYP2D6 metabolism.[8-11] Although CYP2D6 cannot be induced, it is subject to inhibition by a host of medications and may also become saturated. CYP2D6 also exhibits a tremendous amount of genetic variability.[8,12] The clinical significance of CYP2D6 inhibition is variable and can bring about either an increase in active parent drug causing adverse drug effects such as sedation, respiratory depression, and/or death or it can lead to a decrease in active metabolite, resulting in decreased analgesic effects.

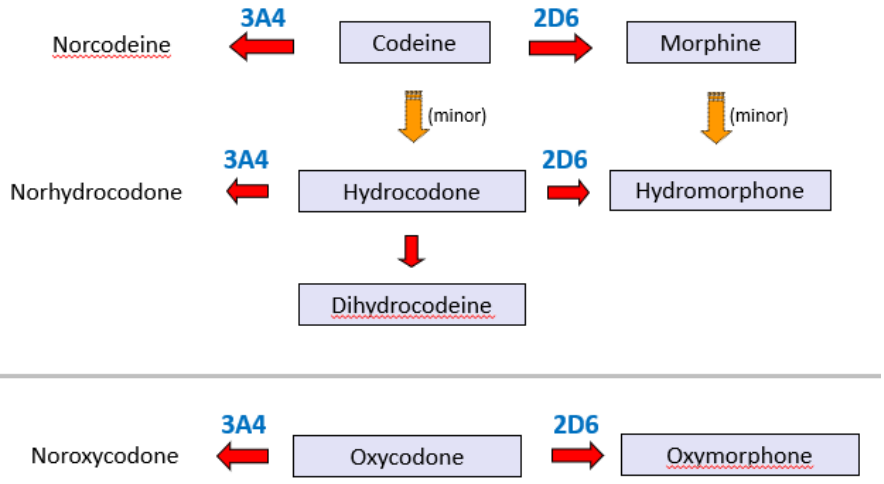
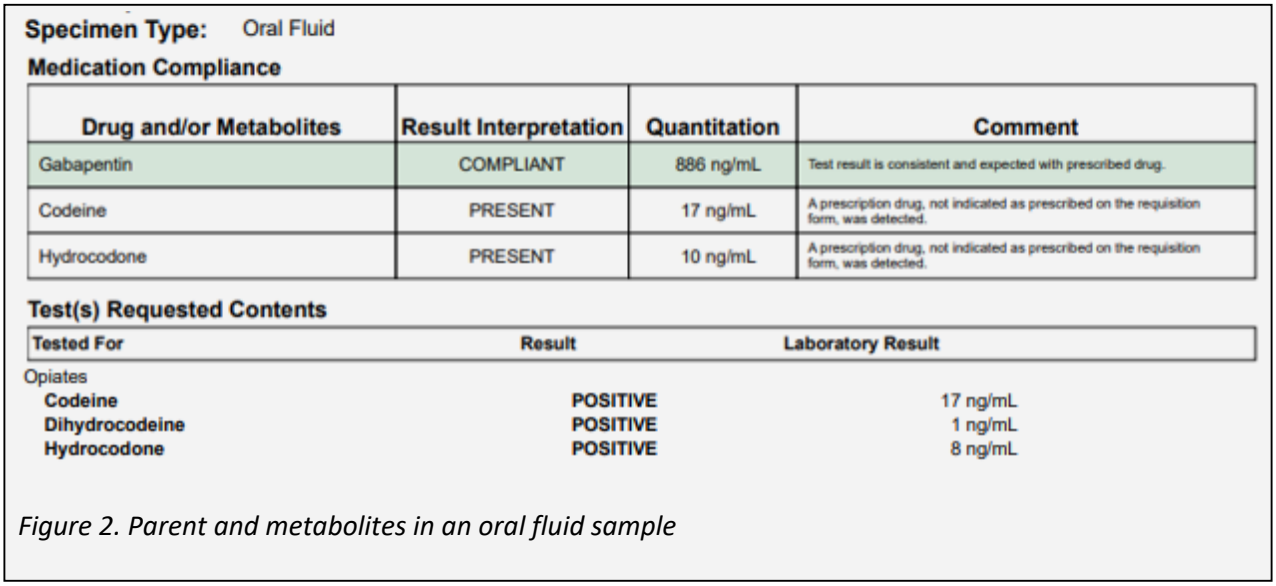


Figure 1. Opioid Metabolism

The period of detection for codeine is based on pharmacokinetic data and drug concentrations found in controlled administration studies, when available. Codeine, and most opioids, typically have a period of detection up to about 5 days in urine and up to about 48 hours in oral fluid. Typically, in oral fluid, parent drug concentrations exceed metabolite concentrations (Figure 2), whereas the reverse is true for urine. However, this is not always the case (Figure 3). Therefore, metabolite ratios should not be used to establish codeine compliance. Concentrations yielded in urine are typically ten times higher than in oral fluid.[13]



Specimen Type: Oral Fluid

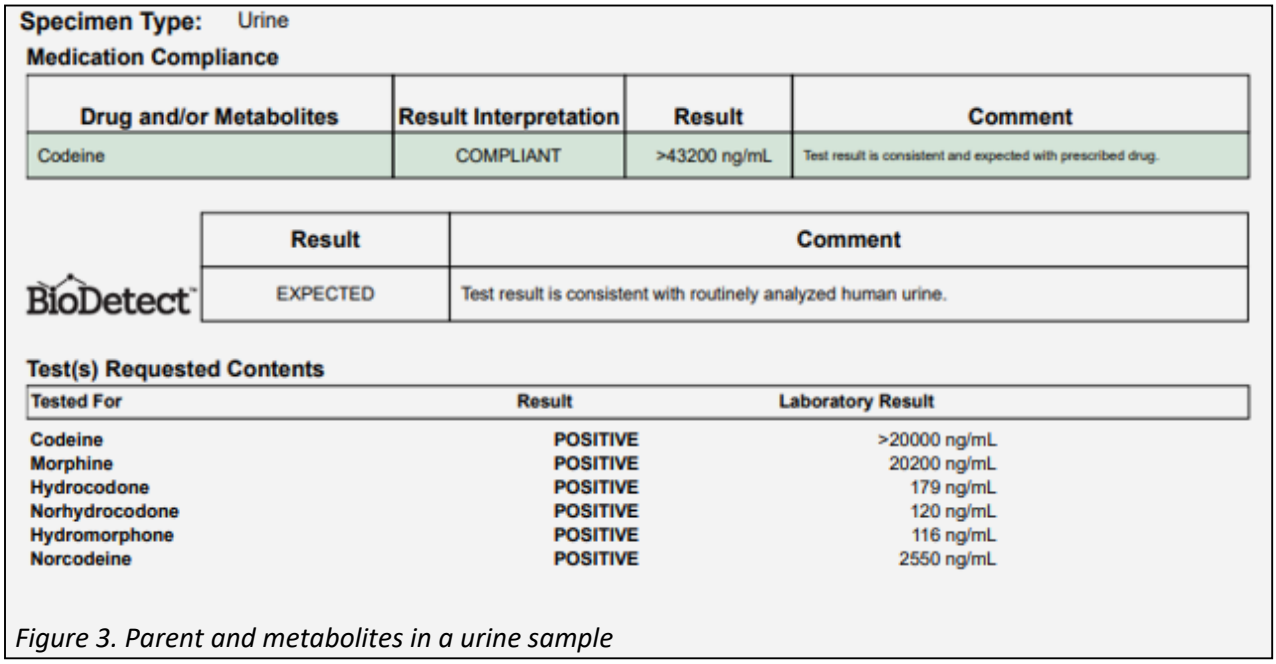
Medication Compliance

Drug and/or Metabolites	Result Interpretation	Quantitation	Comment
Gabapentin	COMPLIANT	886 ng/mL	Test result is consistent and expected with prescribed drug.
Codeine	PRESENT	17 ng/mL	A prescription drug, not indicated as prescribed on the requisition form, was detected.
Hydrocodone	PRESENT	10 ng/mL	A prescription drug, not indicated as prescribed on the requisition form, was detected.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Opiates		
Codeine	**POSITIVE**	17 ng/mL
Dihydrocodeine	**POSITIVE**	1 ng/mL
Hydrocodone	**POSITIVE**	8 ng/mL

Figure 2. Parent and metabolites in an oral fluid sample



Specimen Type: Urine

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Codeine	COMPLIANT	>43200 ng/mL	Test result is consistent and expected with prescribed drug.

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

Test(s) Requested Contents

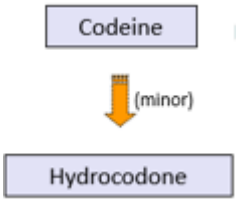
Tested For	Result	Laboratory Result
Codeine	**POSITIVE**	>20000 ng/mL
Morphine	**POSITIVE**	20200 ng/mL
Hydrocodone	**POSITIVE**	179 ng/mL
Norhydrocodone	**POSITIVE**	120 ng/mL
Hydromorphone	**POSITIVE**	116 ng/mL
Norcodeine	**POSITIVE**	2550 ng/mL

Figure 3. Parent and metabolites in a urine sample

There is no validated algorithm that substantiates a correlation between the amount of drug ingested and the amount found in a urine drug screen. Due to the number of factors that can influence the amount of drug eliminated, there can be significant fluctuations in concentrations from test to test in the same patient, and from patient to patient on similar dosages of the same drug. This includes, but is not limited to, concentration of the urine specimen, timing of last dose in relation to collection, frequency of dosing, amount ingested, chronicity of ingestion, extent of drug absorption, liver/kidney function, drug-drug interactions, genetic differences, etc.[14,15]

Codeine Minor Metabolism

Metabolites may be present in the absence of parent drug. For example, a patient who ingests codeine could have only detectable morphine in the urine.[2] Though it would be helpful for interpretation, parent to metabolite ratios do not allow for the identification of the initial opioid ingested. There is, however, one notable exception for codeine: the metabolism of codeine to hydrocodone, which will typically have a concentration of less than 5% of the codeine concentration[16] and should not exceed parent drug concentrations.[2] The enzymes responsible for these metabolic pathways have not been identified, and metabolism may not occur in all patients. The laboratory report example in Figure 4 demonstrates a hydrocodone metabolite concentration of 1.5% of the total codeine concentration in urine.



Specimen Type: Urine

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Codeine	COMPLIANT	36,300 ng/mL	Test result is consistent and expected with prescribed drug.

BioDetect™

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

Test(s) Requested Contents

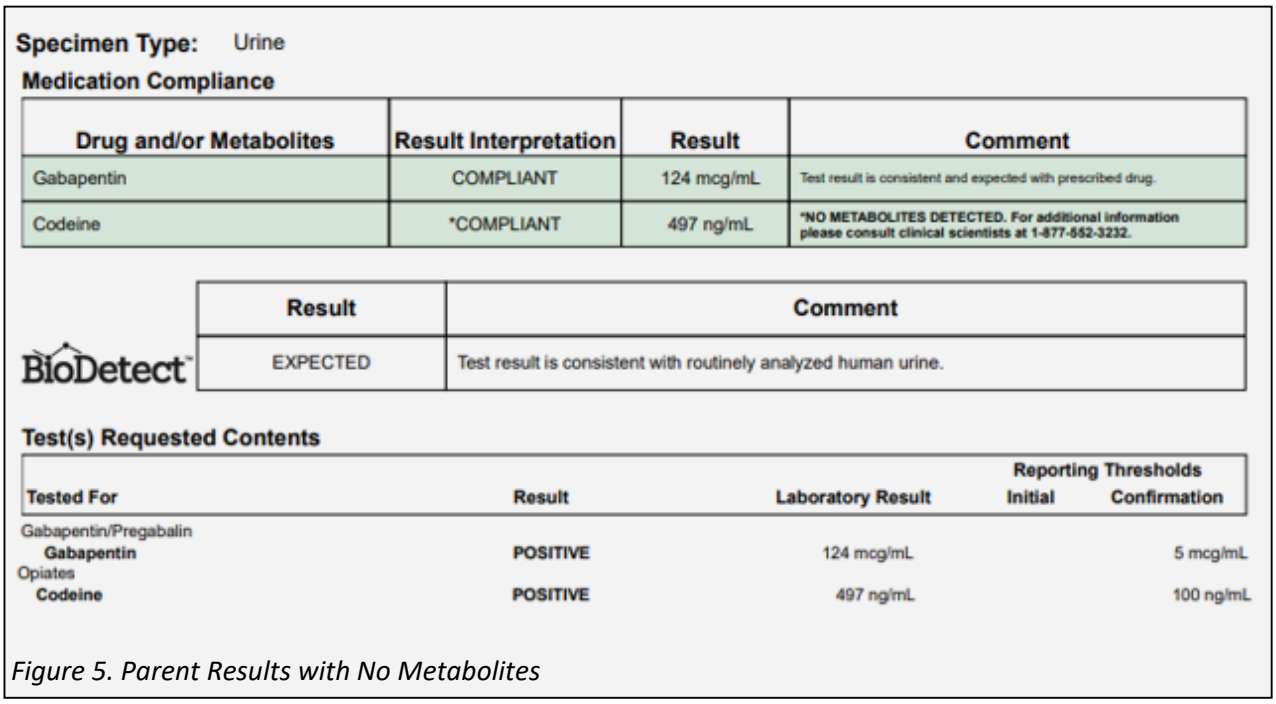
Tested For	Result	Laboratory Result
Codeine	POSITIVE	26500 ng/mL
Morphine	POSITIVE	1300 ng/mL
Hydrocodone	POSITIVE	408 ng/mL
Norhydrocodone	POSITIVE	582 ng/mL
Norcodeine	POSITIVE	7520 ng/mL

Figure 4. Codeine Minor Metabolism Example

Codeine No Metabolites Detected

It is possible to observe parent codeine in urine in the absence of metabolites. The likelihood of such a finding may be increased in patients with impaired metabolism due to genetics or drug-drug/drug-food interactions. Finding parent-only codeine may suggest recent oral drug ingestion, though concentrations in these cases should typically

be low (Figure 5). Additionally, when concentrations are very low, it is difficult to assess if the metabolites may have fallen just below the threshold and, as a result, are reported as negative. On the other hand, when parent-only results are significantly higher (Figure 6), further patient assessment to rule out bingeing or abuse is warranted. Addition of a drug to the sample post-collection, in an effort to appear adherent with prescribed therapy or after sample substitution, may often result in high parent drug urine concentrations with no metabolites present. The clinician should take the laboratory report into consideration with a patient's medication use history and clinical presentation.[17]



Specimen Type: Urine

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Gabapentin	COMPLIANT	124 mcg/mL	Test result is consistent and expected with prescribed drug.
Codeine	*COMPLIANT	497 ng/mL	*NO METABOLITES DETECTED. For additional information please consult clinical scientists at 1-877-552-3232.

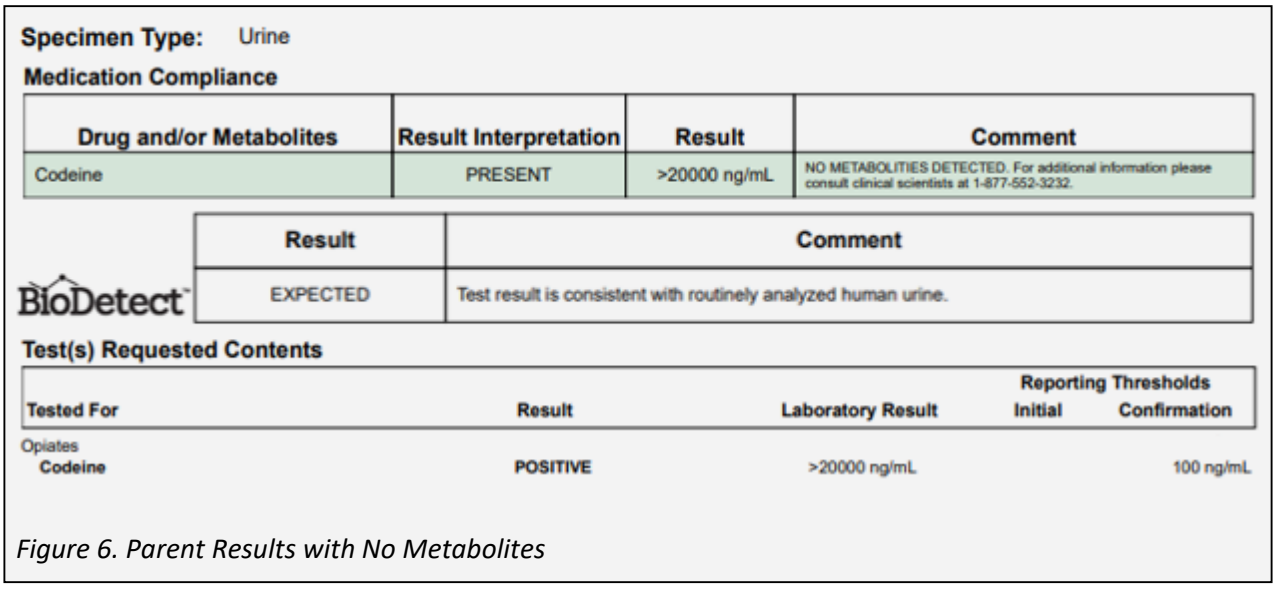
BioDetect™

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

Test(s) Requested Contents

Tested For	Result	Laboratory Result	Reporting Thresholds Initial	Reporting Thresholds Confirmation
Gabapentin/Pregabalin				
Gabapentin	**POSITIVE**	124 mcg/mL		5 mcg/mL
Opiates				
Codeine	**POSITIVE**	497 ng/mL		100 ng/mL

Figure 5. Parent Results with No Metabolites



Specimen Type: Urine

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Codeine	PRESENT	>20000 ng/mL	NO METABOLITIES DETECTED. 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	Reporting Thresholds Initial	Reporting Thresholds Confirmation
Opiates				
Codeine	**POSITIVE**	>20000 ng/mL		100 ng/mL

Figure 6. Parent Results with No Metabolites

Codeine Sources

Patient under-reporting and denial of nonprescribed or illicit drug use are common. However, there are instances when an unexpected positive result has a rational explanation that does not involve extracurricular drug use. It is important to explore all potential sources before enforcing disciplinary action (Table 1). Codeine is present in pharmaceutical products including Tylenol #3; Tylenol #4; Fioricet with Codeine; Pergoric; Tincture of Opium; and Belladona & Opium and will subsequently be present on prescription drug monitoring programs since codeine is a controlled substance. In some states, over-the-counter medications can contain codeine mixed with cough suppressants like dextromethorphan and/or promethazine.[18]

Both codeine and morphine may be present in poppy seeds which can be found in many food products such as breads, muffins, cakes, bagels, salad dressings, and poppy seed enriched curry, as well as commercial or homemade teas.[19,20] Historically, we assume to expect only morphine in urine following poppy seed ingestion as it has been the subject of numerous small studies. Codeine, however, may also be detected, though it tends to appear at significantly lower levels and typically would not be present in the absence of morphine. Small amounts of morphine and/or codeine may be present in oral fluid for two to four hours[21-23] and in urine for up to 48 hours[13] following poppy seed consumption. One notable exception exists in the literature with the case of a subject who consumed bread containing a poppy seed variety with an unusually high codeine-content. The resultant urine specimens contained several times more codeine than morphine, suggesting ingestion of codeine alone.[24] The best advice for patients undergoing drug testing is to completely avoid poppy seed-containing products. Lastly, although the most prevalent metabolite for heroin is morphine, codeine can also result in concentrations above the threshold after heroin use.[25]

DRUG IDENTIFIED	POTENTIAL SOURCES	COMMENTS
Codeine	• Codeine (Tylenol #3®, #4®, Fioricet with Codeine®) • Camphorated Tincture of Opium (Paregoric®) • Tincture of Opium • Belladonna & Opium (B&O) suppositories • Codeine-containing cough suppressants (e.g. Robitussin AC®) • Pharmaceutical impurity in morphine and hydrocodone • Heroin • Poppy seeds	• Pharmaceutical impurity in morphine (up to 0.5%).[2] • Pharmaceutical impurity in hydrocodone (up to 0.15%).[2] • Codeine may be present after use of heroin.[20] • Codeine may be present in urine for several days after ingestion of poppy seeds, typically at lower concentrations than morphine.[12,21] • Following consumption of poppy seeds, codeine may be detected in blood or oral fluid for a few hours.[21,22] • Products containing opium may result in positive findings primarily for morphine, with codeine at lesser concentrations.

NOTICE: The information above is intended as a resource for health care 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.

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