Clinical Update: November 2019

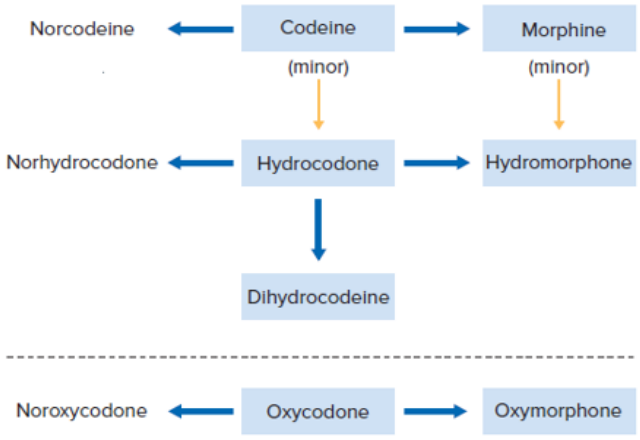
What did my patient actually take? An Overview of Opioid Results Interpretation

Opioids refer to all-natural, semi-synthetic, and fully-synthetic drugs that target the opioid receptors to reduce pain. Morphine and codeine are found naturally in opium. The terms "opiates and semi-synthetic opioids" include drugs such as hydrocodone, oxycodone, hydromorphone, and oxymorphone, which are structurally related to codeine and morphine. Synthetic opioids include drugs such as methadone, fentanyl, meperidine, levorphanol, buprenorphine, and tramadol.

Opioids undergo extensive metabolism, both through cytochrome P450 (CYP450) enzymes (phase 1 metabolism) and glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes (phase 2 metabolism). Pharmacogenetics, drug-drug and drug-food interactions may impact metabolism through these pathways.[1-2]

Metabolism of Opioids

Many prescription opioids are metabolized to other prescribable opioids (see figure below), and this may complicate the interpretation of test results. Though it would be helpful for interpretation, parent to metabolite ratios do not allow for the identification of the initial opioid ingested, with few exceptions. In some circumstances, metabolites may be present in the absence of parent drug; for example, a patient who ingests codeine could have only detectable morphine in urine.[3]



Normetabolites of opioids, such as norcodeine, norhydrocodone, and noroxycodone, are unique biomarkers formed after the use of the corresponding drug (i.e., norcodeine after codeine ingestion) and are products of CYP3A4 metabolism.[3] Although these metabolites possess weak opioid activity, they are not likely to contribute to the overall analgesic effect.[4-6] CYP3A4 metabolism is subject to induction and inhibition by many drug-drug and drug-food interactions, potentially altering opioid normetabolite concentrations.[7-11] Drugs that inhibit or induce the CYP3A4 route of metabolism can modify the effect of opioids, leading to either a decrease in analgesic effects or adverse drug effects such as sedation, respiratory depression, and/or death.

Morphine, hydromorphone, and oxymorphone are pharmacologically active and are products of CYP2D6 metabolism of codeine, hydrocodone, and oxycodone, respectively.[9-12] 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.[9,1] The clinical significance of CYP2D6 inhibition is variable and highly dependent on its role in the metabolism of an opioid. CYP2D6 inhibition can lead to an increase in active parent drug or a decrease in active metabolite leading to either a decrease in analgesic effects or adverse drug effects such as sedation, respiratory depression, and/or death.

The drug testing methodology chosen may directly impact patients, as they may be falsely accused of abusing drugs or not being adherent to their prescribed medications.[13] While point-of-care testing (POCT) can provide timely presumptive results, there are times when a definitive mass spectrometry analyses (LC-MS/MS or GC-MS) is needed to provide the most appropriate patient care.[13]

Example of prescribed hydrocodone on an Aegis lab report:

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Hydrocodone	COMPLIANT	3,080 ng/mL	Test result is consistent and expected with prescribed drug.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Dihydrocodeine	POSITIVE	321 ng/mL
Hydrocodone	POSITIVE	1320 ng/mL
Norhydrocodone	POSITIVE	1130 ng/mL
Hydromorphone	POSITIVE	301 ng/mL

Example of prescribed oxycodone on an Aegis lab report:

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Oxycodone	COMPLIANT	49,400 ng/mL	Test result is consistent and expected with prescribed drug.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Oxycodone	POSITIVE	11300 ng/mL
Oxymorphone	POSITIVE	11800 ng/mL
Noroxycodone	POSITIVE	26200 ng/mL

Minor Opioid Metabolism

Although patients ingesting a parent drug may excrete only metabolite in urine, there are two notable exceptions:

Metabolism of morphine to hydromorphone (see example below)

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Morphine	COMPLIANT	36,400 ng/mL	Test result is consistent and expected with prescribed drug.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Morphine	POSITIVE	36200 ng/mL
Hydromorphone	POSITIVE	223 ng/mL

Metabolism of codeine to hydrocodone (see example below)

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.

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

Both metabolic pathways have the potential to result in small proportions of metabolites, which should not exceed parent drug.[3] The enzymes responsible for these metabolic pathways have not been identified, and metabolism may not occur in all patients. Patients metabolizing codeine to hydrocodone will typically exhibit hydrocodone concentrations under 5% of the codeine concentration in urine.[24] Patients metabolizing morphine to hydromorphone will typically exhibit hydromorphone concentrations under 6% of the morphine concentration in urine.[25-30]

Metabolism of Synthetic Opioids

Synthetic opioid metabolism also often occurs through the CYP450 enzyme system, with varying responsible enzymes (see table below). Most synthetic opioids have a unique metabolite, typically a normetabolite, which may be detected in biologic specimens.

PARENT DRUG	ENZYME	METABOLITE(S)
Buprenorphine	CYP3A4	Norbuprenorphine
	UGT1A1 UGT2B7	Buprenorphine 3-o-glucuronide
Fentanyl	CYP3A4	Norfentanyl
Meperidine	CYP2B6 CYP3A4 CYP2C19	Normeperidine
Methadone	CYP2B6 CYP3A4 CYP2C8 CYP2C19 CYP2D6 CYP2C9	EDDP
Tapentadol	UGT1A9 UGT2B7	Tapentadol-o-glucuronide
	CYP2C9 CYP2C19	Nortapentadol
Tramadol	CYP2D6 CYP2B6 CYP3A4	O-desmethyl-tramadol N-desmethyl-tramadol

Metabolite Patterns in Urine

Due to inter-patient variability, there is a broad range of observable patterns of parent drugs and metabolites in urine and oral fluid. Typically, parent drug concentrations exceed metabolites in oral fluid, whereas in urine, the reverse is true. However, this is not always the case, and metabolite ratios should not be broadly used to establish compliance with prescribed drugs or dosages.

Parent Drug Only/No Metabolites Detected

It is possible to observe parent drug presence 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 compounds may suggest recent oral drug ingestion, though concentrations in these cases should typically be low. It is important to note that in excretion studies of single-dose hydrocodone and oxycodone, most subjects' first urine specimens (0-2 hours after ingestion) had both detectable parent compounds and normetabolites (norhydrocodone and noroxycodone, respectively).[31,32]

Example of no-metabolites detected comment on the Aegis lab report:

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Oxycodone	*PRN - PRESENT	1,300 ng/mL	*NO METABOLITES DETECTED. For additional information please consult clinical scientists at 1-877-552-3232.

Test(s) Requested Contents

Tested For	Result	Laboratory Result
Oxycodone	POSITIVE	1300 ng/mL

Please call our clinical team at 1-877-552-3232 if you require additional information.

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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