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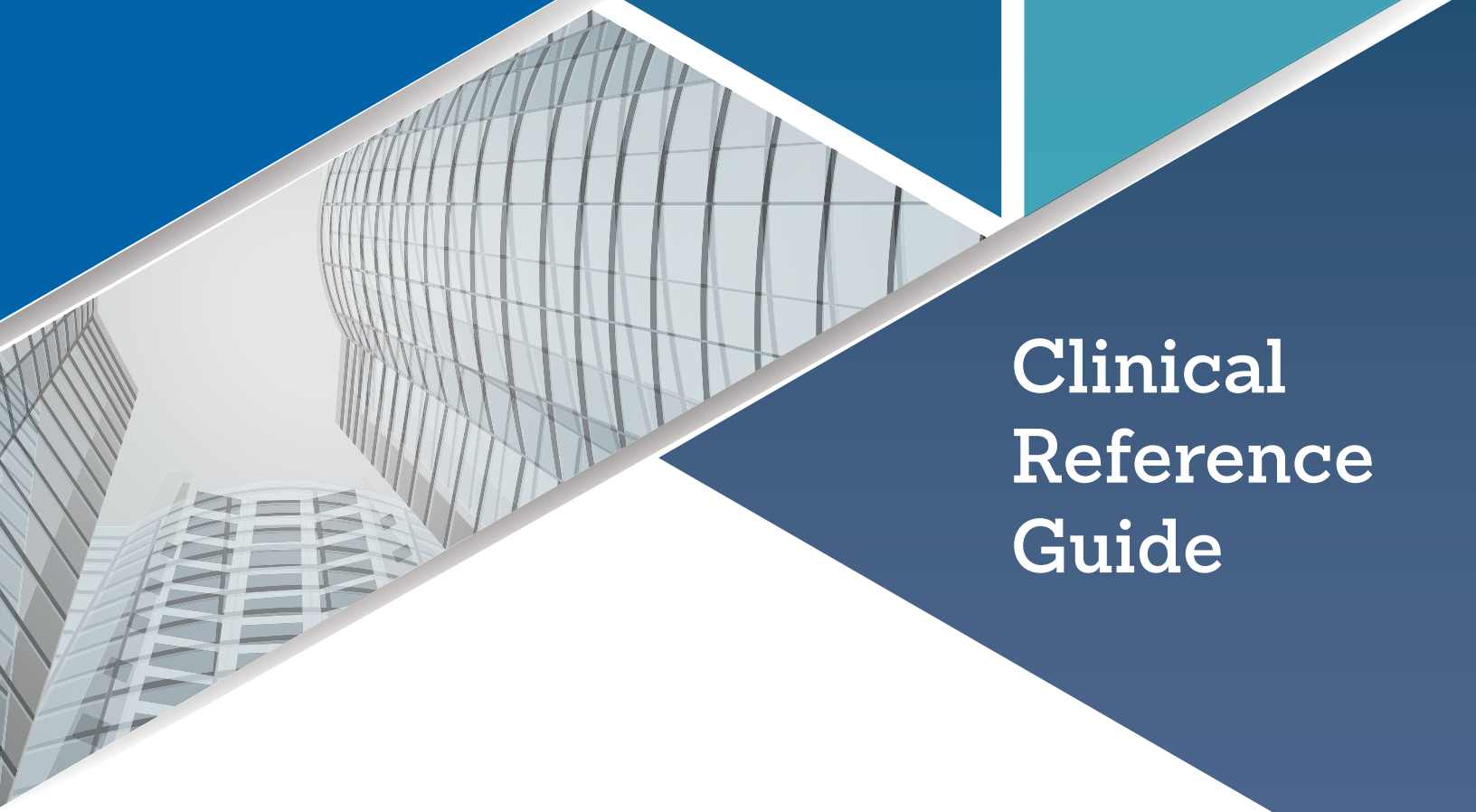


Clinical Reference Guide

Opioid Metabolism

Opioid Metabolism

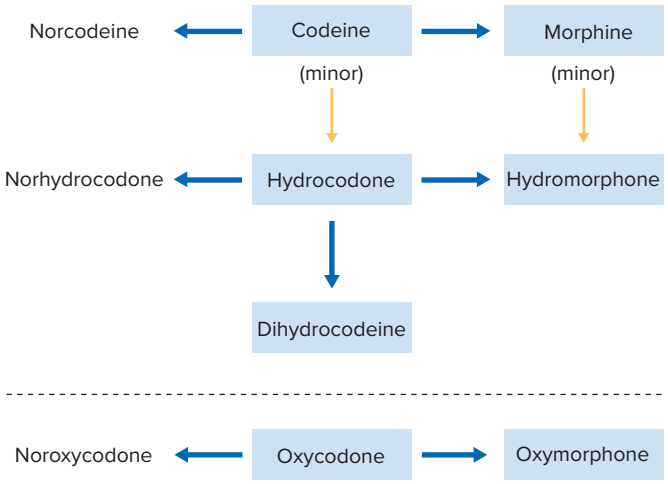
Appropriate interpretation of medication adherence test results requires knowledge of opioid metabolism.

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 and drug-drug/food interactions may impact metabolism through these pathways.[1,2] Laboratories do not always include testing of significant metabolites in their methods. Thus, in these laboratories certain patterns of drug disposition will result in false negatives when urine drug testing is performed.

A. Opioid Metabolism

Many prescription opioids are metabolized to other commercially available opioids (see Figure 12.1), complicating interpretation of test results. Though it would be helpful for interpretation, parent to metabolite ratios do not allow for identification of the initial opioid ingested, with a few exceptions (noted under Section B). 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] These patterns are further discussed in Section C.

Figure 12.1: Opiate Metabolism



Normetabolites of opioids, such as norcodeine, norhydrocodone, and noroxycodone, are unique biomarkers formed after 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]

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. In addition, CYP2D6 exhibits a tremendous amount of genetic variability.[9,13]

Although the CYP450 enzyme system plays a significant role in opiate metabolism, some opiates are metabolized primarily by glucuronidation.[1-3] These include:

- Codeine
- Dihydrocodeine
- Morphine
- Hydromorphone
- Oxymorphone

Synthetic opioid metabolism also often occurs through the CYP450 enzyme system, with varying responsible enzymes (see Table 12.1). Most synthetic opioids have a unique metabolite, typically a normetabolite, which may be detected in biologic specimens.

B. Minor Opiate Metabolism

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

- Morphine metabolism to hydromorphone (hydromorphone to morphine ratio less than 6%)
- Codeine metabolism to hydrocodone (hydrocodone to codeine ratio less than 5%)

Table 12.1: *Synthetic Opioid Metabolism*[14-22]

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

Both metabolic pathways have the potential to result in small proportions of metabolites, which should not exceed parent drug concentrations.[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.[23] Patients metabolizing morphine to hydromorphone will typically exhibit hydromorphone concentrations under 6% of the morphine concentration in urine.[24-29]

There is a paucity of information available to address the prevalence of minor metabolites in oral fluid. It is known that some opiate metabolites are detected in oral fluid.[30-32] A study of 35,000 oral fluid specimens from pain patients indicated unexpected low concentrations of minor metabolites alongside positives for prescribed opiates: specifically, hydromorphone was present in 10.6% of patients positive for prescribed morphine, and hydrocodone in 40.5% of patients positive for prescribed codeine.[32] A more recent study described hydrocodone as being the most commonly detected metabolite of codeine in oral fluid samples positive for codeine with codeine indicated as prescribed.[33]

C. 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 used to establish adherence 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/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).[34,35] In a study of 39,700 urine specimens from patients receiving treatment for pain, 2.9% of tested specimens contained parent drug in the absence of metabolites; the majority of these findings were concentrations greater than the median concentration observed for that drug. The highest number of parent-only findings occurred for oxycodone (2.4% of all oxycodone results), followed by hydrocodone (1.6% of all hydrocodone results).[36] These findings may suggest post-collection addition of drugs to urine, in an effort to appear adherent with prescribed treatment.

Metabolite Patterns

As previously mentioned, metabolites, particularly opioid normetabolites, are often present in absence of parent drug. This may also be true for other opiate metabolites (e.g., hydromorphone from hydrocodone metabolism, or oxymorphone from oxycodone metabolism).

A single-dose hydrocodone excretion study of 12 subjects indicated that hydrocodone and norhydrocodone typically appeared in urine within 1-2 hours, followed by hydromorphone and dihydrocodeine within 2-4 hours.

Concentrations were highest for norhydrocodone, followed by hydrocodone, hydromorphone, and dihydrocodeine. Though norhydrocodone-only results were common in this study, occurring in 23% of specimens, one specimen was positive for hydromorphone-only during the terminal elimination phase. Although hydromorphone and dihydrocodeine concentrations often fell below hydrocodone and norhydrocodone concentrations, hydromorphone concentrations did exceed other markers in some specimens.[35] Other studies of urinary data suggest that the metabolism of hydrocodone to hydromorphone via CYP2D6 may be saturable.[37]

Following single-dose administration of oxycodone controlled-release 20 mg, oxycodone and noroxycodone appeared within 0-2 hours, followed by oxymorphone and noroxymorphone. Oxycodone was most often accompanied by noroxycodone presence. Of note, five (3.8%) specimens contained only oxymorphone with no other markers present. Such results make it difficult to distinguish which opiate was ingested.[34] Testing for norhydrocodone and noroxycodone extends the period of detection versus testing for parent compounds alone.[34,35]

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