PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #307
OPIOID PHARMACOKINETICS

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Background Pharmacokinetics is the science of what the body does to a drug after administration, in contrast to pharmacodynamics -- the effect of a drug on the body. Knowledge of opioid pharmacokinetics parameters is critical for the safe and effective administration.

Absorption The proportion of active drug (whether given intravenously or absorbed from the gastrointestinal, respiratory, or cutaneous system) that enters the systemic circulation is defined as bioavailability. The wide bioavailability range amongst different opioids is partially attributable to differences in first pass metabolism, when the drug is metabolized directly by the liver from the gastrointestinal tract before it reaches the systemic circulation. Clinicians should be aware of the bioavailability for the opioid being prescribed because it indirectly affects PO: IV conversion ratios.

Distribution refers to the movement of drug between the blood and various tissues in the body. The parameter used to describe this movement is the volume of distribution (Vd). The targeted tissue for opioids is the central nervous system (CNS). To activate the targeted receptors, opioids must cross the blood-brain-barrier (1). Those opioids with a higher Vd are usually more lipophilic, and more likely to distribute faster and more strongly both into and out of the blood-brain-barrier. In clinical practice these opioids also tend to have a quicker onset, and shorter duration of analgesic action.

Metabolism The most important area of opioid pharmacokinetics is metabolism. The metabolism process may involve the Cytochrome (CYP) P-450 enzymes, particularly CYP 2D6 and 3A4, or other enzymes such as UDP-glucuronyltransferase (2). The spectrum of interpatient analgesic variability and clinically significant drug interactions of opioids are mostly due to the CYP enzymes.

Interpatient Variability CYP 2D6 influences the metabolism of codeine, hydrocodone, oxycodone, and tramadol, and has been found to have many genetic polymorphisms. Based on phenotypic profiles, patients can be poor, intermediate, or extensive metabolizers (3). This can potentially lead to inadequate analgesia or over-sedation. Fentanyl and methadone are primary metabolized by CYP 3A4. Although CYP 3A4 also has many genetic polymorphisms, none have be shown to be of major clinical relevance (4). UDP-glucuronyltransferase, the primary enzyme responsible for the metabolism of morphine, hydromorphone, oxymorphone, and tapentadol, does not possess significant interpatient variability.

Clinically Significant Drug Interactions There are three types of CYP P-450 enzyme subcategories: substrates, inhibitors, and inducers. Substrates require P-450 enzymes for metabolism. When enzyme inhibitors or inducers are concomitantly administered with substrates, the serum levels of these substrates are altered. Enzyme inhibitors may increase opioid serum levels leading to over-sedation; enzyme inducers may decrease opioid serum levels leading to inadequate analgesia. Table 1 summarizes drug interactions between opioids and commonly prescribed medications (5).

Enzyme	Substrates	Inhibitors	Inducers
CYP 3A4	Codeine, fentanyl, methadone, oxycodone, tramadol	Amiodarone, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, itraconazole, ketoconazole, nefazodone, ritonavir, verapamil, voriconazole	Carbamazepine, dexamethasone, efavirenz, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifampin, St. John's wort, troglitazone

CYP 2D6	Codeine, hydrocodone, methadone, morphine, oxycodone, tramadol	Amiodarone, bupropion, celecoxib, chlorpromazine, citalopram, diphenhydramine, doxepin, duloxetine, escitalopram, fluoxetine, haloperidol, hydroxyzine, metoclopramide, paroxetine, quinidine, ritonavir, sertraline, terbinafine, thioridazine	None reported

Excretion The vast majority of opioids are excreted as metabolites through the kidneys, with the exception of methadone which is primarily excreted via bile. Patients with renal and/or liver dysfunction may have altered drug clearance (see *Fast Facts* #161 and #260). Clinicians should be aware of opioid-individual terminal elimination half-lives (T ½), as these dictate the speed of opioid titrations. When given consistently, opioids reach steady state after four T½. Opioid titrations should be avoided until the opioid regimen has reach steady state.

Summary Table 2 summarizes the pharmacokinetic parameters of commonly used oral opioids. These parameters are critical for the safe and effective use of these medications, as they commonly translate into individual pharmacodynamics properties (6-17).

Opioid (Route)	**Absorption**	**Distribution**	**Metabolism**		**Excretion**	
	Bioavailibility (%)	Vd (L/kg unless noted)	Major Metabolism Enzyme (s)	Active Metabolite	Urine (%)	T ½ (Hours)
Codeine (PO)	53	3-6	CYP3A4 and 2D6	Morphine	90	3
Fentanyl (TDS)	N/A	4-6	CYP3A4	None	75	20-27
Hydrocodone IR (PO) ð	NR	NR	CYP2D6 and 3A4	Hydromorphone	26	3.3-4.4
Hydro-morphone IR (PO)	24	4	UGT	Unknown	75	2-3
Methadone (PO)	36-100	1-8	CYP3A4, 2D6, 2B6, 2C19	None	<10	7-59
Morphine IR (PO)	<40	4	UGT	M6G	90	2-4
Oxycodone IR (PO)	60-87	2.6	CYP3A4 and 2D6	Oxymorphone	19-64	2-4
Oxymor-phone IR (PO)	10	1.94-4.22 L	UGT	6-OH	33-38	7-9
Tramadol IR (PO)	75	2.6	CYP3A4 and 2D6	M1	90	6.3
Tapentadol IR (PO)	32	540 +/- 98 L	UGT	None	99	4-5

Key: PO: oral; TDS: transdermal system; IR: immediate-release; δ: hydrocodone IR is available only in combination with acetaminophen; Vd: Volume of distribution; L: liters; N/A: non-applicable; CYP: Cytochrome enzyme; UGT: UDP-glucuronosyltransferase; M6G: Morphine-6-glucuronide; 6-OH: 6-OH-Oxymorphone; M1: O-desmethyltramadol; NR: not reported

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