Drug Metabolism

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Many opioid and other analgesic agents are subject to metabolism and elimination via a variety of hepatic enzymes. These elimination pathways may be directly related to impaired or excessive pharmacologic responses, depending on the coadministration of other medications capable of inducing, inhibiting, or competing for access to these enzymes, creating significant drug interactions. The following tables identify many of the important pathways involved in analgesic metabolism and may be useful references for determining drug interactions.

Opioid Analgesics

Opioid	PG Risk* Factor	CYP Substrate	CYP Inducer	CYP Inhibitor
Alfentanil	C	3A4		
Buprenorphine	C	3A4		1A2, 2A6, 2C19
Butorphanol	C/D			2D6
Codeine	C/D	2D6, 3A4		2D6
Dihydrocodeine	B/D	2D6		
Fentanyl	C/D	3A4		3A4
Hydrocodone	C/D	2D6		
Hydromorphone	C/D	Phase II glucuronidation conjugated 6-OH minor metabolites		
Levorphanol	B/D	Hepatic		
Meperidine	C/D	2B6, 2C19, 3A4		
Methadone	C/D	3A4, 2C9, 2C19, 2D6		2D6, 3A4
Morphine	C/D	Phase II, 2D6 (minor)		
Nalbuphine	B/D	Hepatic		
Oxycodone	B/D	2D6		
Oxymorphone	C	Phase II glucuronidation		
Pentazocine	C/D	Oxidation, glucuronidation		
Propoxyphene	C/D	2D6	2D6	
Remifentanil	C	Unknown CYP450 nonspecific esterases (blood) and tissue		2D6
Sufentanil	C	3A4		
Tramadol	C	2B6, 2D6, 3A4		

Other Agents with a Disease-State-Specific Analgesic Indication

Other Analgesics	PG Risk Factor	Substrate	CYP Inducer	CYP Inhibitor
Duloxetine	C	1A2, 2D6	IA2	1A2, 2D6
Gabapentin	C	almost not metabolized		
Pregabalin	C	almost not metabolized		

The Nonsteroidal Antiinflammatory Drugs (NSAIDs)

NSAIDs	Metabolic Substrate Pathway	Cyp450 Inhibitor	Pg Category
Acetic acid derivatives			
Diclofenac (plus misoprostol) Diclofenac	3A4, misoprostol: rapid de-esterification to free acid 2C9, 3A4	2C9, 2E1, 3A	X C
Etodolac	Hepatic		D/C
Indomethacin	2C9, 2C19	2C9, 2C19	C/D
Sulindac	Hepatic, prodrug (sulfide to sulfone)		C/D
Tolmetin	Conjugation inactive metabolite		C/D
Carboxylic acids			
Aspirin (acetylsalicylic acid, ASA)	GI mucosa, RBC, spinal fluid, blood		C/D
Buffered aspirin	Esterase		C/D
Choline magnesium trisalicylate	Similar to above/ASA		C/D
Diflunisal	Saturable hepatic pathway to glucuronides		C/D
Enteric-coated salicylates	Salicylate metabolism		C/D
Salsalate	Hepatic conjugation		C/D
Fenamates			
Enolic acids			C/D
Meclofenamate Hepatic	Hepatic		C/D
Mefenamic	2C9	2C9	C/D
Meloxicam	2C9, 3A4		C/D
Piroxicam			C/D
Naphthylamines			
Celecoxib (Sulfonamide)	2C9, 3A4	2D6, 2C8	C/D
Extoracoxib	3A4		C/D
Lumiracoxib	2C9		C/D
Nabumetone	Hepatic-prodrug to 6 MNA extensive 1st pass		C/D
Selective COX-2 inhibitors			C/D
Propionic acids			
Fenoprofen	Extensive hepatic		C/D
Flurbiprofen	2C9	2C9	C/D
Ibuprofen	2C9, 2C19	2C9	C/D
Ketoprofen	Phase II, enterohepatic recirculation		C/D
Naproxen; Enteric	1A2, 2C9		C/D
Oxaprozin	CYP Oxidation		C/D

The Non-NSAIDs Analgesic

Acetaminophen (APAP)	1A2, 2A6, 2C9, 2D6, 2E1, 3A4	3A4	B

**C/D=Prolonged Use, High Dose at Term*