

Practical Pharmacokinetics: Opioids and Adjuvants

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Disclosure

In the past 12 months, Dr. Kral has received an honorarium from PriCara Pharmaceutical Company for a speaker training program.



Outline

- Absorption
 - Distribution
 - Metabolism
 - Elimination
- NSAIDs,
Salicylates,
Acetaminophen
Antidepressants
Anticonvulsants
Opioids
Other



Factors affecting Pk

- Genetics
- Race/ethnicity
- Age
- Organ function
- Co-morbidities
- Gender/Pregnancy

●●● | Absorption – GI tract

- Passive
 - Buccal
 - Transmucosal
 - Rectal
- Active
 - Carrier-protein mediated

●●● | Absorption – Transdermal vs. Topical

- Rate of absorption depends on:
 - Skin thickness and integrity
 - Medication lipophilicity
 - Vascularity
 - Skin temperature
 - SQ fat (?)
- Medications incorporated into PLO (lipid) base to increase absorption.

●●● | Absorption: NSAIDs, salicylates, acetaminophen

- Most are readily absorbed from GI tract
- Absorption via rectal route variable
- Some undergo 1st pass metabolism
- Also readily absorbed transdermally
 - Diclofenac
 - Ibuprofen
 - Salicylates

●●● | Absorption: Antidepressants

- Most are rapidly absorbed from the GI tract
- Most undergo extensive 1st pass metabolism, reducing bioavailability
- Topical amitriptyline and doxepin have shown some efficacy for depression, pain and itching.

Scott MA. Pharmacotherapy 1999;19(2):236
McCleane G. B J Clin Pharmacol 2000;49(6):574

Absorption: Anticonvulsants – 1st generation

- Phenytoin
 - Good absorption but variable
 - All products are not equal
- Carbamazepine
 - Well absorbed, but slow
- Valproic acid
 - Rapid absorption
 - All forms converted to valproic acid in gut

Absorption: Anticonvulsants- 2nd generation

- Most are readily absorbed from GI tract
- Gabapentin actively absorbed via amino acid transport system in gut
 - May become saturated
 - Bioavailability dec. as dose inc.
- No data supporting topical use

Garnett W. Clinical Pharmacokinetics 4th. ASHP

Absorption: Opioids

- Most oral formulations are well absorbed
- Many have reduced bioavailability due to 1st pass metabolism
 - Morphine, meperidine, hydromorphone
 - Liver disease increases bioavailability
- Transmucosal
 - More effective with lipophilic agents
- Rectal
 - Morphine absorption similar to oral

Tegeder I. Clin Pharmacokinet 1999;37(1):17.

Absorption: Transdermal/topical

- Local anesthetics
 - Very little absorption into blood stream with intact skin
 - Lidocaine
- Ketamine
- Clonidine
- Capsaicin

Distribution

- Plasma proteins
 - AAG
 - Albumin
 - Dependent upon nutritional status, liver disease
- Lipophilicity - passive transport accumulation in tissues
- Active transport across membranes
 - P-gp

Distribution:

NSAIDs, salicylates, acetaminophen

- NSAIDs – distributed widely
 - Celecoxib highly protein bound
- Salicylates highly protein bound
 - May have problems with displacement
 - Depends on albumin concentration
 - Distribute readily into synovial fluid
- Acetaminophen widely distributed
 - Low plasma protein binding

Distribution: Antidepressants

- >80% plasma protein bound
- Highly lipophilic
- Passive transport through membranes (e.g. BBB)
- Accumulate in tissues (e.g. CNS)

Distribution: Anticonvulsants

- All widely distributed
- All readily penetrate the BBB into the CNS
- Plasma protein binding varies
 - <10% with gabapentin, pregabalin
 - >90% phenytoin
 - Variable binding with valproic acid

Distribution: Opioids

- Plasma protein binding varies
 - < 10% codeine, 70-80% methadone
- Large Vd – distributed into all highly perfused tissues
- Lipophilic – fentanyl family
 - Rapid transport into CNS
 - May accumulate in tissues
- Hydrophilic – morphine, hydromorphone
 - Slower transport into CNS

Metabolism – Phase I

- Cytochrome P450 enzymes
 - Oxidation, reduction, hydrolysis
 - CYP2, CYP3
 - Small intestine – first-pass metabolism
 - Liver
 - Affected by liver disease
 - Affected by other meds that induce or inhibit the enzymes

Metabolism – Phase II

- Less affected by liver disease
- Makes compounds more water soluble
- Glucuronidation, sulfation, acetylation and methylation

Drug-Drug Interactions

- Usually CYP450 enzyme *inhibition* occurs within 2-3 days
 - Reversible within 2-3 days
- *Induction* may take 2-3 weeks
 - Reversal may take weeks
 - Carbamazepine
 - Phenytoin
 - St. John's wort
 - Fluoxetine/paroxetine/sertraline

Metabolism: Antidepressants

- Undergo extensive first-pass metabolism
- All undergo Phase 1 hepatic metabolism
- Many have active metabolites
 - Amitriptyline →
 - Imipramine →
 - Fluoxetine →
 - Venlafaxine →
- Several are CYP450 enzyme inhibitors

Metabolism: Anticonvulsants – 1st generation

- Carbamazepine
 - Classic inducer of CYP450 3A4
 - Phase I oxidation
- Phenytoin
 - Inducer of CYP450 3A4
 - Phase I oxidation, saturable
 - Zero-order kinetics
- Valproic acid
 - Phase I and Phase II metabolism

Metabolism: Anticonvulsants – 2nd generation

- Gabapentin, pregabalin - not metabolized
- Lamotrigine – Phase II to inactive metab
- Topiramate – minimal, mixed metab
 - Inhibits phenytoin and valproic acid
 - Induced by phenytoin, carbamazepine
- Oxcarbazepine – no liver metabolism
 - Inhibits CYP2C19
 - May induce UGT (Phase II)

Metabolism: Opioids

Phase I – via hepatocellular enzymes

- | | |
|-------------------|-----------------|
| ○ CYP2D6 activity | ○ CYP3A family |
| ● Codeine | ● Fentanyl |
| ● Tramadol | ● Tramadol |
| ● Hydrocodone | ● Buprenorphine |
| ● Oxycodone | ● Oxycodone |
| ● Methadone | ● Methadone |

Smith H. Mayo Clinic Proc 2009;84(7):613.

Metabolism: Opioids

Phase II – glucuronidation

- Morphine
 - M-6-glucuronide
 - M-3-glucuronide
- Hydromorphone
 - H-3-glucuronide
- Oxycodone

Smith H. Mayo Clinic Proc 2009;84(7):613.

Factors Affecting Opioid Metabolism

TABLE 3. Demographic/Medical Factors Influencing Opioid Metabolism

Opioid	Age	Sex	Ethnicity	Hepatic impairment	Renal impairment
Morphine ¹⁰	Clearance may be reduced in older patients	No effect	Chinese patients have higher clearance of morphine	Dose adjustment recommended	Dose adjustment recommended
Codeine ¹⁰	Caution recommended in older patients	No effect	CYP2D6 allelic variants may alter metabolism; more common in populations of Asian or African descent	Dose adjustment recommended	Dose adjustment recommended
Hydrocodone ¹⁰	Caution recommended in older patients	No known effect	CYP2D6 allelic variants may alter metabolism; more common in populations of Asian or African descent	Most frequently administered in combination with acetaminophen; liver function monitoring is advised during treatment in patients with hepatic impairment	Most frequently administered in combination with acetaminophen; liver function monitoring is advised during treatment in patients with severe renal impairment
Oxycodone ¹⁰	Concentrations normally higher in older patients	Concentrations ~25% higher in women than in men	No effect	Dose adjustment recommended	Dose adjustment recommended
Meperidine ¹⁰	Dose adjustment may be necessary in elderly patients	No effect	No effect	Dose adjustment recommended in patients with severe impairment	Dose adjustment recommended in patients with severe impairment
Tramadol ¹⁰	Effects of age on pharmacokinetics have not been studied	No significant effect	No effect	Pharmacokinetics significantly altered in patients with severe hepatic impairment	Pharmacokinetics significantly altered only in patients with severe renal impairment
Fentanyl ¹⁰	Clearance may be reduced in older patients	No effect	No effect	Dose adjustments may not be necessary in patients with hepatic impairment	Dose adjustments may not be necessary in patients with renal impairment
Hydrozepam ¹⁰	No effect	C _{max} ~25% higher in women than in men with similar AUC _{0-∞}	Concentrations the same in men and women after controlling for body weight	Dose adjustment recommended	Dose adjustment recommended
Oxycodone ¹⁰	Steady-state concentrations ~60% higher in patients aged ≥65 y	No effect	No effect	Contraindicated in patients with moderate or severe hepatic impairment	Dose adjustment recommended

AUC_{0-∞} = area under the plasma concentration vs time curve; C_{max} = maximum plasma concentration; CYP = cytochrome P450.

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Elimination

- Hepatic dysfunction
 - Reduces 1st pass metabolism
 - Reduces Phase 1 metabolism
- Renal dysfunction
 - Renal failure
 - Hemodialysis

Elimination: NSAIDs

- Caution with hepatic impairment
- NSAIDs should not be used with renal impairment
- Salicylates readily removed by HD
- Caution with acetaminophen use in hepatic or renal impairment

Elimination: Antidepressants

- Reduce dose with liver impairment
- Very little renal elimination
- Terminal half-lives ~ 24 hours
- May have pharmacologic activity for weeks
- Blood levels are variable and not correlated with analgesia
- Reduced clearance in elderly

Elimination: Anticonvulsants

- Reduce dose with liver impairment
 - Valproic acid, lamotrigine, topiramate
- Reduce dose with renal impairment
 - Gabapentin, pregabalin, topiramate, oxcarbazepine

Elimination: Opioids

- Reduce dose with liver impairment
 - Morphine, hydromorphone, oxycodone, fentanyl, methadone
- Reduce dose with renal impairment
 - Morphine, hydromorphone
 - Avoid meperidine
 - No adjustment necessary with fentanyl and methadone

Case 1

- PP is taking gabapentin and tramadol for diabetic neuropathy. She is demonstrating symptoms of depression.
- Which antidepressant is safest?

Case 2

- GR is POD#2 after a hemicolectomy. He had a larger intra-op blood loss than expected. He has chronic back pain and his home medication, morphine was restarted post-op. The nurses report at shift change that he is quite somnolent and RR is 8 bpm.
- What might have happened to GR?

Case 3

- TH has been taking a stable dose of methadone for > 6 months. She saw a new provider for her migraines and was started on topiramate 3 days ago and seemed to do well. She is somnolent today.
- What could be causing her symptoms?

