Opioid Analgesics

April 16, 2018
Mark Beenhakker, Pharmacology
markbeen@virginia.edu

Glossary

Opium: dried, condensed juice of the poppy flower *Papaver somniferum*
Opiate: compounds that are structurally related to products found in opium
Opioid: any substance, regardless of structure, that has functional/pharmacological properties of an opiate
Endogenous opioids: **(1)** naturally occurring opioids found in the body, **(2)** includes 3 primary families: endorphins, enkephalins, and dynorphins
Opioid receptors: **(1)** μ (MOR), **(2)** κ (KOR), **(3)** δ (DOR), **(4)** all GPCRs (G protein-coupled receptors)
MOR: **(1)** μ opiate receptor that is the target of most opiate analgesics, **(2)** activation leads to (a) opening of potassium channels (causes negative shift in neuron voltage – aka 'hyperpolarization'), (b) closing of calcium channels (inhibits release of neurotransmitter), and (c) inhibits cAMP
Morphine: **(1)** potent opiate analgesic, **(2)** most abundant alkaloid found in opium, (3) not as lipophilic as some high-potency opioids (e.g. heroin, fentanyl)
Codeine: **(1)** weak to midrange analgesic, **(2)** 2nd most abundant alkaloid found in opium, **(3)** also used for antitussive (cough suppressant) and antidiarrheal properties
Heroin: **(1)** opioid analgesic synthesized by adding acetyl groups to morphine molecule (i.e. diacetylmorphine), **(2)** very lipid soluble and, therefore, rapidly penetrates CNS, **(3)** a pro-drug
Fentanyl: **(1)** very lipophilic, potent synthetic opioid (100-1000X more potent than morphine), **(2)** can be administered via skin patch (because lipophilic), **(3)** short-acting (when given orally)
Methadone: synthetic opioid used as analgesic and to treat opiate dependency
Oxycodone: semi-synthetic opioid
Oxycontin: slow-release form of oxycodone
Pentazocine: partial MOR agonist
Buprenorphine: partial MOR agonist
Naloxone: **(1)** MOR antagonist used for opiate overdose, **(2)** very little oral bioavailability, **(3)** short T1/2
Naltrexone: **(1)** MOR antagonist primarily used for opiate addiction, **(2)** can be taken orally, **(3)** longer T1/2 than naloxone
Nalmefene: **(1)** more 'universal' opioid antagonist (i.e. blocks MORs, KORs and DORs), **(2)** primarily used for alcohol dependence
Pain: perception of an aversive/unpleasant sensation
Nociception: transmission of signals to the CNS that provide information about tissue damage
DRG: **(1)** dorsal root ganglion (or spinal ganglion), **(2)** collection of neuronal cell bodies whose axons relay sensory information into the CNS (i.e. afferents), **(3)** DRG neurons terminate in the dorsal horn of the spinal cord
Aδ fiber: **(1)** nociceptive afferent that is thinly myelinated, **(2)** activation of Aδ fibers is associated with sharp, prickly pain, **(3)** widely distributed in the skin and in deep tissue
C fiber: **(1)** nociceptive, polymodal afferent that is not myelinated, **(2)** activated by a variety of high-intensity mechanical, chemical, and hot/cold stimuli, **(3)** widely distributed in the skin and in deep tissue

Ascending pathways: (1) relay nociceptive input from the dorsal horn of the spinal cord to higher centers in the brain, **(2)** major 'tracts' include spinothalamic, spinoreticular, and spinomesencephalic tracts

Hyperalgesia: **(1)** when sensation of pain in response to subsequent stimuli is enhanced, **(2)** occurs when peripheral tissues are damaged, **(3)** involves the release of many chemical mediators (e.g. histamine, bradykinin, prostaglandins, etc) that act to lower the threshold of nociceptor activation

Periaqueductal Gray (PAG): **(1)** mesencephalic structure that plays a large role in descending modulation of pain, **(2)** expresses a high density of MORs, **(3)** opioid administration directly into the PAG blocks nociceptive responses

Myenteric Plexus: **(1)** complex intrinsic meshwork of neuron cell bodies and their nerve fibers that constitute a major part of the enteric nervous system, **(2)** provides motor innervation to the GI tract, **(3)** morphine reduces output of myenteric plexus, thereby decreasing gut motility (i.e. constipation)

Catecholamine: group of monoamine neurotransmitters that include epinephrine, norepinephrine and dopamine

Dopamine: catecholamine that plays a major role in reward-driven learning

Ventral Tegmental Area (VTA): **(1)** mesencephalic (midbrain) brain structure that contains drug and reward circuitry, **(2)** origin of the mesolimbic dopaminergic system

Nucleus Accumbens: **(1)** part of the limbic portion of the basal ganglia (base of forebrain) that contains drug and reward circuitry, **(2)** receives dopaminergic input from the VTA

Epidural: **(1)** or 'epidural analgesia', **(2)** injection of drug into epidural space (space within the spinal canal lying *outside* the dura mater), **(3)** regional form of analgesia

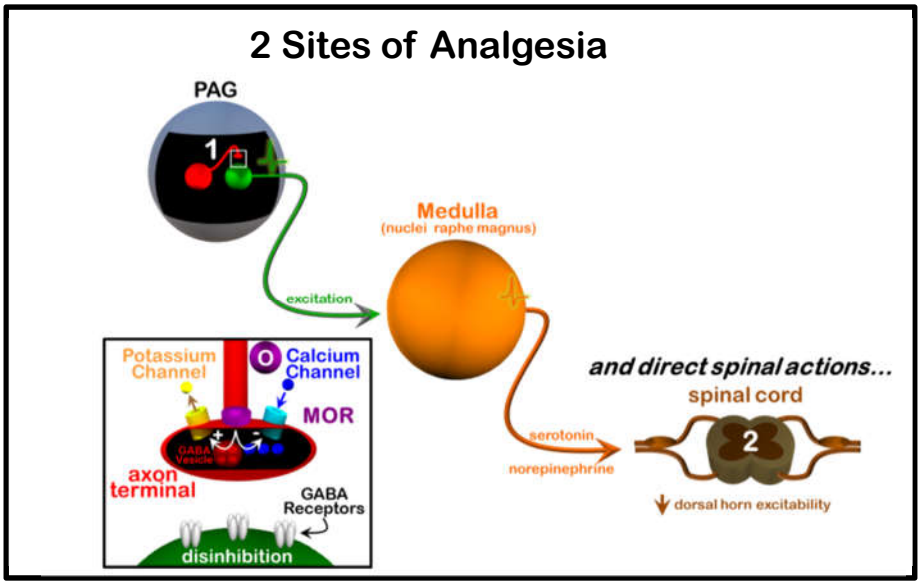
Intrathecal: **(1)** or 'intrathecal analgesic', **(2)** injection of drug *within* the dura mater of spinal canal, **(3)** more direct route than epidural, **(3)** regional form of analgesia

General Points

1. Effects of Morphine

a. Analgesia

i. Results from actions at many levels of the neuraxis (e.g. mesencephalic PAG, spinal cord)



ii. Primarily results from activation of MORs
iii. Occurs without loss of consciousness
iv. Normal sensory modalities are much less altered
v. The alagesic effects of opiates are usually additive with those of the NSAIDs (non-steroidal anti-inflammatory drugs, e.g. asparin, ibuprofen)

b. Respiratory depression

i. Morphine decreases the respiratory pattern generator found in the brain stem
ii. Detectable in the low therapeutic range and with increasing dose
iii. May be lethal in patients with compromised respiration
iv. Less respiratory depression associated with epidural/intrathecal administration

c. Decreased gut mobility

i. Gut (myenteric plexus) is one of the major sites of morphine action
ii. Morphine decreases propulsive peristaltic contractions, leading to an antidiarrheal effect.
iii. Also decreases urinary voiding reflex – catheterization may be required with therapeutic doses of morphine.

d. Peripheral vasodilation

i. Hypotensive effects are correlated with posture:
    1. Little effect in recumbent, normovolemic patient
    2. Can cause orthostatic hypotension
ii. Hypotensive effects can be very serious in hypovolemic patients

2. Absorption, Distribution and Excretion

a. Absorption: morphine is readily absorbed from the GI tract, nasal mucosa and lungs

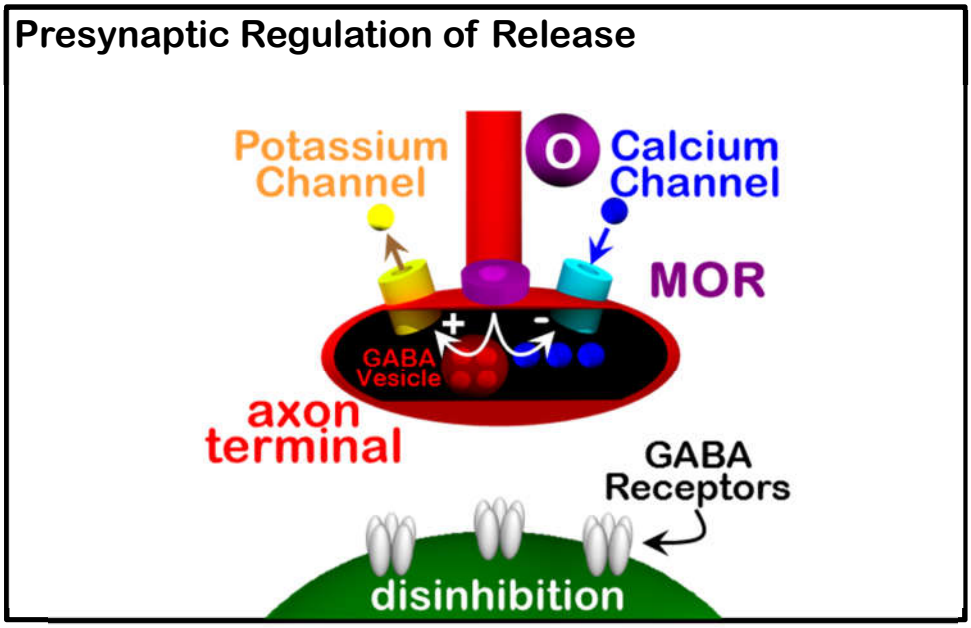
b. Distribution: morphine **(1)** does not accumulate in the tissue, **(2)** has short plasma T1/2, **(3)** conjugated with glucuronic acid in liver

c. Excretion: 90% urinary, 10% biliary

3. Mechanisms

a. Opens potassium channels: causes negative shift in voltage of neuron so that neuron is less excitable

b. **Closes calcium channels**: reduces neurotransmitter release (vesicular release of neurotransmitter is calcium-dependent)



c. **Actions in PAG**: mechanism (a) above primarily acts on inhibitory neurons in the PAG, thereby reducing output of inhibitory neurons. This releases excitatory neurons in the PAG from inhibitory forces (i.e. 'disinhibition') and enables them to activate descending analgesia systems.
d. **Actions in spinal cord**: mechanisms (a) and (b) act in dorsal horn to decrease dorsal horn excitability

4. Tolerance and Dependence

a. Tolerance is pharmacodynamic
    i. Tolerance to one opiate agonist produces tolerance to all others (i.e. 'cross tolerance')
b. Physical dependence is prominent
    i. Withdrawal from opiates is less severe than that from ethanol and barbiturates.
c. Agonists (e.g. methadone) are used in 'Replacement' or 'Maintenance' therapy
    i. Keeps individual tolerant and dependent but helps break habit
        1. Taken orally – helps break injection habit

2. Taken once/day or less
3. Long T1/2 so does not produce serious withdrawal

ii. Partial MOR agonists (e.g. Buprenorphine) sometimes used
1. Can actually antagonize the effects of heroin/high potency agonists but has some of the benefits of methadone because receptors are still activated

Useful Tables from Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th Edition

Opioid Agonist Actions/Selectivities at μ,δ, & κ receptors *(Goodman & Gilman's, page 483)*

Table 18–1

Actions and Selectivities of Some Opioids at μ, δ, and κ Receptors

	RECEPTOR TYPES		
OPIOID LIGANDS	μ	δ	κ
Agonists			
Etorphine	+++	+++	+++
Fentanyl	+++		
Hydromorphone	+++		+
Levorphanol	+++		
Methadone	+++		
Morphine[a]	+++		+
Sufentanil	+++	+	+
DAMGO[a] ([D-Ala^2,MePhe^4,Gly(ol)^5]enkephalin)	+++		
DPDPE[b] ([D-Pen^2,D-Pen^5]enkephalin)		++	
[D-Ala^2,Glu^4]deltorphin		++	
DSLET ([D-Ser^2,Leu^5]enkephalin-Thr^6)	+	++	
SNC80		++	
Bremazocine	+++	++	+++
Buprenorphine	P		– –
Butorphanol	P		+++
Ethylketocyclazocine	P	+	+++
Nalbuphine	– –		++
Spiradoline[c]	+		+++
U50,488[c]			+++
U69,593[c]			+++
Endogenous Peptides			
Met-enkephalin (**Tyr-Gly-Gly-Phe-Met**)	++	+++	
Leu-enkephalin (**Tyr-Gly-Gly-Phe-Leu**)	++	+++	
β-Endorphin (**Tyr-Gly-Gly-Phe-Met**-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu)	+++	+++	
Dynorphin A (**Tyr-Gly-Gly-Phe-Leu**-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln)	++		+++
Dynorphin B (**Tyr-Gly-Gly-Phe-Leu**-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr)	+	+	+++
α-Neoendorphin (**Tyr-Gly-Gly-Phe-Leu**-Arg-Lys-Tyr-Pro-Lys)	+	+	+++
Endomorphin-1 (Tyr–Pro–Trp–Phe–NH_2)	+++		
Nociceptin (orphanin FQ) (Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln)	–	–	–

Opioid Antagonist Actions/Selectivities at μ,δ, & κ receptors *(Goodman & Gilman's, page 484)*

Table 18–1

Actions and Selectivities of Some Opioids at μ, δ, and κ Receptors (*Continued*)

OPIOID LIGANDS	RECEPTOR TYPES		
	μ	δ	κ
Antagonists			
Naloxone[d]	– – –	–	– –
Naltrexone[d]	– – –	–	– – –
CTOP[a]	– – –		
Diprenorphine	– – –	– –	– – –
β-Funaltrexamine[a,c]	– – –	–	++
Naloxonazine	– – –	–	–
nor-Binaltorphimine	–	–	– – –
Naltrindole[b]	–	– – –	–
Naloxone benzoylhydrazone	– – –	–	–

[a]Protoypical μ-preferring. [b]Prototypical δ- preferring. [c]Prototypical κ- preferring. [d]Universal ligand. [e]Irreversible ligand. +, agonist; –, antagonist; P, partial agonist. The number of symbols is an indication of potency; the ratio for a given drug denotes selectivity. These values are obtained primarily from a composite overview of results obtained in vivo/in vitro animal pharmacological work and in ligand binding and activity studies and should be extrapolated to humans with caution.

Source: Reproduced with permission from Raynor et al, 1994.

Opioid Analgesic Dosing *(Goodman & Gilman's, page 498)*

Table 18–2

Dosing Data for Clinically Employed Opioid Analgesics

DRUG	APPROXIMATE EQUI-ANALGESIC ORAL DOSE	APPROXIMATE EQUI-ANALGESIC PARENTERAL DOSE	RECOMMENDED STARTING DOSE (adults >50 kg) ORAL	RECOMMENDED STARTING DOSE (adults >50 kg) PARENTERAL	RECOMMENDED STARTING DOSE (children and adults <50 kg)[a] ORAL	RECOMMENDED STARTING DOSE (children and adults <50 kg)[a] PARENTERAL
Opioid Agonists						
Morphine[b]	30 mg q3–4h (around-the-clock dosing) 60 mg q3–4h (single dose or intermittent dosing	10 mg q3–4h	15 mg q3–4h	5 mg q3–4h	0.3 mg/kg q3–4h	0.1 mg/kg q3–4h
Codeine[c]	130 mg q3–4h	75 mg q3–4h	30 mg q3–4h	30 mg q2h (IM/SC)	1 mg/kg q3–4h[d]	Not recommended
Hydromophone (DILAUDID)[b]	7.5 mg q3–4h	1.5 mg q3–4h	4 mg q3–4h	1 mg q3–4h	0.06 mg/kg q3–4h	0.015 mg/kg q3–4h
Hydrocodone (in LORCET, LORTAB, VICODIN, others, typically with acetominophen)	30 mg q3–4h	Not available	5 mg q3–4h	Not available	0.2 mg/kg q3–4h[d]	Not available
Levorphanol	4 mg q6–8h	2 mg q6–8h	2 mg q6–8h	1 mg q6–8h	0.04 mg/kg q6–8h	0.02 mg/kg q6–8h
Meperidine (DEMEROL)	300 mg q2–3h	100 mg q3h	Not recommended	50 mg q3h	Not recommended	0.75 mg/kg q2–3h
Methadone (DOLOPHINE, others)	20 mg q6–8h	10 mg q6–8h	2.5 mg q12h	2.5 mg q12h	0.2 mg/kg q12h	0.1 mg/kg q6–8h
Oxycodone (REXICODONE, OXYCONTIN, also in PERCOCET, PERCODAN, TYLOX, others)[g]	30 mg q3–4h	Not available	5 mg q3–4h	Not available	0.2 mg/kg q3–4h[d]	Not available
Oxymorphone[b] (NUMORPHAN)	Not available	1 mg q3–4h	Not available	1 mg q3–4h	Not recommended	Not recommended
Propoxyphene (DARVON)	130 mg[e]	Not available	65 mg q4–6h[e]	Not available	Not recommended	Not recommended
Tramadol[f] (ULTRAM)	100 mg[e]	100 mg	50–100 mg q6h[e]	50–100 mg q6h[e]	Not recommended	Not recommended
Opioid Agonist–Antagonists or Partial Agonists						
Buprenorphine (BUPRENEX)	Not available	0.3–0.4 mg q6–8h	Not available	0.4 mg q6–8h	Not available	0.004 mg/kg q6–8h
Butorphanol (STADOL)	Not available	2 mg q3–4h	Not available	2 mg q3–4h	Not available	Not recommended
Nalbuphine (NUBAIN)	Not available	10 mg q3–4h	Not available	10 mg q3–4h	Not available	0.1 mg/kg q3–4h

Published tables vary in the suggested doses that are equi-analgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical response is necessary. Because there is not complete cross-tolerance among these drugs, it is usually necessary to use a lower than equianalgesic dose when changing drugs and to retitrate to response. *Caution*: Recommended doses do not apply to patients with renal or hepatic insufficiency or other conditions affecting drug metabolism and kinetics. [a]*Caution*: Doses listed for patients with body weight less than 50 kg cannot be used as initial starting doses in babies less than 6 months of age. Consult the *Clinical Practice Guideline for Acute Pain Management: Operative or Medical Procedures and Trauma* section on management of pain in neonates for recommendations. [b]For morphine, hydromorphone, and oxymorphone, rectal administration is an alternate route for patients unable to take oral medications, but equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences. [c]Caution: Codeine doses above 65 mg often are not appropriate due to diminishing incremental analgesia with increasing doses but continually increasing constipation and other side effects. [d]Caution: Doses of aspirin and acetaminophen in combination opioid/NSAID preparations must also be adjusted to the patient's body weight. Maximum acetaminophen dose: 4 g/day in adults, 90 mg/kg/day in children. [e]Doses for moderate pain not necessarily equivalent to 30 mg oral or 10 mg parenteral morphine. [f]Risk of seizures; parenteral formulation not available in the U.S. [g]Oxycontin is an extended-release preparation containing up to 160 mg of oxycodone per tablet and recommended for use every 12 hours. It has been subject to substantial abuse. Modified from Agency for Healthcare Policy and Research, 1992.

Epidural/Intrethecal Dosing *(Goodman & Gilman's, page 514)*

Table 18–3

Epidural or Intrathecal Opioids for the Treatment of Acute (Bolus) or Chronic (Infusion) Pain

DRUG	SINGLE DOSE (mg)[a]	INFUSION RATE (mg/h)[b]	ONSET (min)	DURATION OF EFFECT OF A SINGLE DOSE (h)[c]
Epidural				
Morphine	1-6	0.1-1.0	30	6-24
Meperidine	20-150	5-20	5	4-8
Methadone	1-10	0.3-0.5	10	6-10
Hydromorphone	1-2	0.1-0.2	15	10-16
Fentanyl	0.025-0.1	0.025-0.10	5	2-4
Sufentanil	0.01-0.06	0.01-0.05	5	2-4
Alfentanil	0.5-1	0.2	15	1-3
Subarachnoid (Intrathecal)				
Morphine	0.1-0.3		15	8-24+
Fentanyl	0.005-0.025		5	3-6

[a]Low doses may be effective when administered to the elderly or when injected in the thoracic region.
[b]If combining with a local anesthetic, consider using 0.0625% bupivacaine. [c]Duration of analgesia varies widely; higher doses produce longer duration. With the exception of epidural/intrathecal morphine or epidural sufentanil, all other spinal opioid use is considered to be off label.
Adapted from International Association for the Study of Pain, 1992.

Where Opioids Fall in Pain Managment *(Goodman & Gilman's, page 519)*

Table 18–8

Summary of Drug Target and Site of Action of Common Drug Classes and Relative Efficacy by Pain State

DRUG CLASS (REPRESENTATIVE AGENTS IN PARENTHESES)	DRUG ACTION	SITE OF ACTION[a]	RELATIVE EFFICACY IN PAIN STATES[b]
NSAIDs (ibuprofen, aspirin acetominophen)	Nonspecific COX inhibitors	Peripheral and spinal	Tissue injury >> acute stimuli = nerve injury = 0 (Hamza and Dionne, 2009, Svensson and Yaksh, 2002)
COX 2 inhibitor (celecoxib)	COX2-selective inhibitor	Peripheral and spinal	Tissue injury >> acute stimuli = nerve injury = 0 (Hamza and Dionne, 2009)
Opioids (morphine)	μ receptor agonist	Supraspinal and spinal	Tissue injury = acute stimuli ≥ nerve injury > 0 (see this chapter)
Anticonvulsants (gabapentin)	Na^+ channel block, $\alpha_2\delta$ subunit of Ca^{2+} channel	Supraspinal and spinal	Nerve injury > tissue injury = acute stimuli = 0 (Lai et al., 2004; Taylor, 2009)
Tricyclic antidepressants (amitryptiline)	Inhibit uptake of 5-HT/NE	Supraspinal and spinal	Nerve injury ≥ tissue injury >> acute stimuli = 0 (Mochizucki, 2004)

[a]Studies based on local delivery in preclinical models, e.g., intracranial microinjection or intraventricular injections, lumbar intrathecal delivery or topical/sq application at injury site. [b]Pain states are defined by preclinical models: acute: hot plate/tail flick/acute mechanical compression; tissue injury: intraplantar injections of irritants, focal thermal injury; nerve injury: compression/ligation of sciatic nerve or its branches or of nerve roots; systemic delivery of chemotherapeutics. See Mogil, 2009.