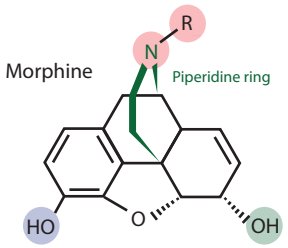
OPIOIDS

Opiates are drugs derived from the the opium plant, Papaver somniferum which contains morphine, codiene, thebaine and many other alkaloids. An opioid is a much more general term which referes to all substances which bind opioid receptors. Opioids exert both peripheral and central anlagesic actions and they act on pain without interfering with objective sensations such as touch and temperature. As noted on the previous page pain is made up of two components, fast and slow pain. The fast pain is carried in through the neospinothalamic pathways and conducts well-localised objective aspects of painful sensations. Slow pain is transmitted rostrally more slowly becuase of extensive synaptic interactions in the brainstem and limbic structures. It is poorly localised and responsible for the hurt or suffering associated with pain. Opioid drugs specifically target slow pain. Patients will often report that the pain is still there but the hurt is gone.

Opioid receptors are members of the family of G protien coupled receptors. There are three major classes of opioid receptors μ, δ, and κ. In general the opioid receptors are inhibitory, acting primarily through the $G_{i\alpha}$ and $G_{o\alpha}$ classes of G Protien. They inhibit andenylyl cyclase (μ, δ, and κ) and can also stimulate K^+ channel activity (μ and δ) and inibit Ca^{2+} channel activity (κ). They are present on both pre and post synaptic terminals. Although they share their ability to elict spinal and supraspinal analgesia, their pharmacologic properties differ. Most of the clinically used opioids including methadone and the fentanyl series are relatively selective for μ receptors, reflecting their similarity to morphine. The effects include analgesia, constipation and respiratory depression. Studies involving the use of the opioid antagonist naloxonazine and the potent morphine metabolite morphine-6β-glucuronide (M6G) have revealed at least three distinct subtypes of the μ receptor. The δ receptor are divided into two known subtypes have similar effects to μ receptor but there are no agents acting on δ receptors available clinically. There are three κ subtypes. Although several of the highly selective κ_1 produced analgesic effects the accompanying side effects have prevented their development. These side effects include a significant diuretic action, psychotomimetic effects and dysphoria. The utilisation of the κ receptor is limited to the mixed agonist/antagonist drugs.

Endogenous opioid peptides Pharmacologically endogenous peptides share many characteristics including the ability to produce analgesia. They are stored in vesicles and upon release bind to the G Protien coupled opioid recptors. Endorphins exert their effects at all three receptors. The recently discovered endomorphins have uniquely high selectivity for μ receptors. The δ receptors are highly selective for enkephalins. Dysnorphins are endogenous ligands for the K receptors. Regional differences exist in the distribution of the various opioid peptides within the CNS. The enkaphalins are widely distributed, implying a wide range of actions beyond simple analgesia. In contrast the β-endorphin is limited to the pituitary and arcuate region of the hypothalamus, although these areas have extensive projections. Although it unclear whether they act as classic neurotransmitters, they appear to inhibitory modulation at many sites peripherally, spinally and supraspinally.



Structure activity relationship The most opioids have the general phenanthrene structure composed of a three ring nucleus, an additional piperidine ring and a tertiary amine (red). Most of the substitution and variability occurs at the coloured areas. In particular codiene is a morphine prodrug and this involves the removal of a methyl group at position 3 (coloured in blue) and replacement with the hydroxyl group shown. This occurs via CYP2D6 and absence of this reduces codiene effect.

Therapeutic and adverse effects of opioids

Miosis - caused by excitatory action on parasympathetic nerve innervating the pupil

Nausea and vomiting produced by morphine-like drugs are caused by direct stimulation of the chemoreceptor trigger zone in the area postrema of the medulla.

Cough Morphine and related opioids also depress the cough reflex, at least partly by direct action on a cough center in the medulla.

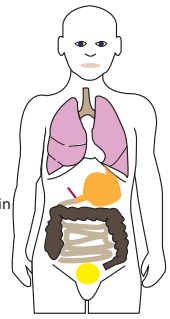
Stomach Morphine and other mu agonists usually decrease gastric acid secretion and decrease motility prolonging digestion times

Biliary tract After the subcutaneous injection of 10 mg morphine sulfate, the sphincter of Oddi constricts, and the pressure in the common bile duct may rise more than tenfold within 15 minutes; this effect may persist for 2 hours or more.

Small Intestine Morphine diminishes biliary, pancreatic, and intestinal secretions and delays digestion of food in the small intestine.

Large Intestine Propulsive peristaltic waves in the colon are diminished or abolished after administration of morphine, and tone is increased to the point of spasm.

Urinary may cause urinary retention



Nervous System produces analgesia and modulation of the pain response in peripheral, spinal and supraspinal locations. May produce both euphoria and dysphoria. Decreases Level of consciousness and may cause confusion. Can induce psychosis.

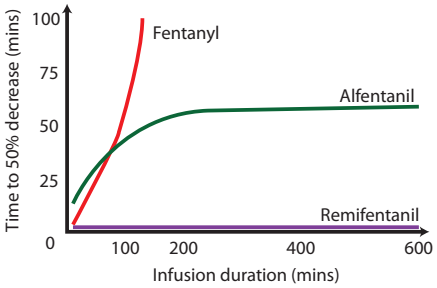
Respiratory system - caused by two mechanisms, direct inhibition of the respiratory centre and indirectly by decreased consciousness

Cardiovascular system In the supine patient, therapeutic doses of morphine-like opioids have no major effect on blood pressure or cardiac rate and rhythm. Such doses do produce peripheral vasodilation, reduced peripheral resistance, and an inhibition of baroreceptor reflexes. Therefore, when supine patients assume the upright position, orthostatic hypotension and fainting may occur, although this is usually only in combination with pre-existing instability.

Musculoskeletal system may cause muscle rigidity which can impair respiratory function by decreasing chest wall compliance.

Skin Therapeutic doses of morphine cause dilation of cutaneous blood vessels. The skin of the face, neck, and upper thorax frequently becomes flushed. These changes may be due in part to the release of histamine and may be responsible for the sweating and pruritus that occasionally follow the systemic administration of morphine.

Routes of administration The lipid solubility of opioids largely determines the speed of onset and duration of intrathecal analgesia; hydrophilic drugs (eg morphine) have a slower onset of action and longer half-lives in cerebrospinal fluid with greater dorsal horn bioavailability and greater cephalad migration compared with lipophilic opioids. Because of the hydrophilic nature of morphine, there is rostral spread of the drug in cerebrospinal fluid (CSF), and side effects, especially respiratory depression, can emerge up to 24 hours later as the opioid reaches supraspinal respiratory control centers.The behaviour of epidural opioids is also governed largely by their lipid solubility. The greater sequestration of lipid soluble opioids into epidural fat and slow re-release back into the epidural space means that elimination from the epidural space is prolonged, resulting in relatively smaller fractions of drug reaching the cerebrospinal fluid. Lipophilic opioids (eg fentanyl) have a faster onset but shorter duration of action compared with hydrophilic drugs (eg morphine). Transdermal routes of administration are also determined by lipid solubility (hence the use of fentanyl patches). There is a significant first pass metabolism with morphine (60-70%), therefore is often delivered via SC, IM or buccally.



Comparative pharmacology The duration of effect is dependent on the mechanism of administration, rate of clearance, active metabolites and lipid solubility. Highly lipid soluble opioids rapidly cross the BBB and therefore have higher potency, but because they rapidly distribute they often have a rapid offset in action (bolus fentanyl). Low lipid soluble drugs like morphine have a longer duration of action.

The pKa determines the % ionised at physiological pH and therefore drugs such as alfentanil with a low pKa is mostly non-ionised at 7.4 therefore are able to cross the BBB quickly as well increasing the speed of onset.

Fentanyl has similar pharmacokinetics to thiopentone, it is rapidly distributed to tissues due to its high lipid solubility but it has a slow clearance. As a result it has a short duration of action if given as a bolus (redistribution), but repeat dosing leads to a markedly higher duration of action due to an increased context sensitive half time.

	Morphine	Pethidine	Fentanyl	Alfentanyl	Remifentanil
pKa	8.0	8.5	8.4	6.5	7.1
%Non-Ionised (pH = 7.4)	23	5	9	95	68
%Protein Binding	30	40	84	90	70
Terminal β1/2	3	4	3.5	1.6	0.05
Clearance ml/kg/min	15-30	8-18	10-20	4-9	30-40
VdSS (l/kg)	3-5	3-5	3-5	0.4-1.0	0.2-0.3
Relative lipid solubility	1	28	580	90	50
Relative potency	1	0.36	50-100	20	50-100
Equivalent dose 10mg morphine	10mg	28mg	0.1-0.2mg	0.5-1.0 mg	0.1-0.2mg

Remifentanil has a unique metabolic and pharmacokinetic profile. It undergoes rapid methyl ester hydrolysis by tissue and plasma esterases (not plasma cholinesterase) to relatively inactive metabolites, as a result its effect is terminated by metabolic clearance rather than redistribution. This results in a rapid reduction in plasma concentration even during prolonged infusions and this is independent of age, weight, sex, hepatic or renal function.

Dose equivalence is shown adjacent. Morphine is three times as potent IV compared to PO due to bioavailability. Oxycodone and methadone and equipotent. Codiene is 10-15 times weaker. Tramadol is 10 times weaker. It should be noted that there is significant inter and intra-patient variability and changing agents when a patient is tolerant to one opioid they may be less tolerant to another regardless of equivalence.

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