Pharmacology of Opioids

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DEFINITIONS
Opium   A mixture of alkaloids from the poppy plant - Papaver somniferum.

Opioid   Any naturally occurring, semi-synthetic or synthetic compound that binds specifically to opioid receptors (see below) and shares the properties of one or more of the naturally occurring endogenous opioids.

Opiate   Any naturally occurring opioid derived from opium (e.g. morphine).

Narcotic   From the Greek meaning 'to numb or deaden'. It is often used to denote an opioid but also widely used to describe drugs of addiction and hence includes non-opioid compounds.

MECHANISM OF ACTION
Opioids produce their actions at a cellular level by activating opioid receptors. These receptors are distributed throughout the central nervous system (CNS) with high concentrations in the nuclei of tractus solitarius, peri-aqueductal grey area (PAG), cerebral cortex, thalamus and the substantia gelatinosa (SG) of the spinal cord. They have also been found on peripheral afferent nerve terminals and many other organs. The efficacy of centrally applied opioids is well recognized, but when applied peripherally, for example in post-traumatic and inflammatory states, their actions are less reliable. Opioid receptors are coupled with inhibitory G-proteins and their activation has a number of actions including: closing of voltage sensitive calcium channels; stimulation of potassium efflux leading to hyperpolarization and reduced cyclic adenosine monophosphate production. Overall, the effect is a reduction in neuronal cell excitability that in turn results in reduced transmission of nociceptive impulses.

Pure opioid agonists (morphine, diamorphine, pethidine and fentanyl) bind to opioid receptors avidly and demonstrate high intrinsic activity at the cellular level as described above. Partial opioid agonists (buprenorphine, pentazocine) bind to opioid receptors, but produce a sub-maximal effect compared to pure agonists and so have less intrinsic activity associated with receptor binding. Opioid antagonists (naloxone, naltrexone), have receptor affinity but no intrinsic activity.

OPIOID RECEPTORS
Since their identification, opioid receptors have had a variety of names. The following is the current nomenclature for identification of the opioid receptors, approved by the International Union of Pharmacology.

MOP - μ (mu) opioid peptide receptor

KOP - κ (kappa) opioid peptide receptor

DOP - δ (delta) opioid peptide receptor

NOP (nociceptin orphanin FQ peptide receptor)

The sigma receptor is no longer classified as an opioid receptor as it does not meet all the criteria to be described as one. A number of different subtypes of each receptor exist; two MOP, three KOP, and two DOP subtypes.

OPIOIDS
Naturally occurring opioid compounds are found in plants (e.g. morphine) and produced in the body (endogenous opioids), where they are widely distributed throughout the central nervous system (CNS). These endogenous compounds are peptides that have variable potency and are preferentially bound by different opioid receptors. They have numerous actions including modulation of pain and control of the cardiovascular system, particularly in shock. Although of interest to pharmacologists, endogenous opioids currently have no clinical role. Synthetic and semi-synthetic opioids are widely used clinically, primarily for their analgesic actions. They exert their effect via the same receptors. Endogenous opioid peptides and commonly used opioid drugs, along with their selectivity (affinity) for different types of opioid receptors, are shown in Table 1.

CLASSIFICATION OF OPIOIDS
Several classifications have been proposed (Table 2).

- **Traditional** - based upon analgesic potency
- **Origin of drug** - i.e. naturally occurring or manufactured

Summary
Opioid drugs are widely used as moderate to strong analgesic agents. The pharmacokinetic properties of different agents determine their analgesic and side effect profiles. Many agents that have fallen from favour in more developed countries are still widely used in poorly-resourced settings and so knowledge of their advantages and disadvantages is essential.

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Table 1. *Opioids and their selectivity for different opioid receptors*

Opioid	Receptor type			
	MOP	**KOP**	**DOP**	**NOP**
Endogenous				
Beta-endorphin	+++	+++	+++	-
Leu-enkaphalin	+	-	+++	-
Dynorphin A& B	++	+++	+	+
OFQ	-	-	-	+++
Clinical drugs				
Agonists				
Morphine	+++	+	+	-
Pethidine	+++	+	+	-
Diamorphine	+++	+	+	-
Fentanyl	+++	+	-	-
Partial agonists				
Buprenorphine	++	+	-	-
Pentazocine	-	++	-	-
Antagonists				
Naloxone	+++	++	++	-
Naltrexone	+++	++	++	-

+ = low affinity, ++ = moderate affinity, +++ = high affinity, - = no affinity.

• **Function** - their action at the opioid receptor.

In the traditional classification, the 'strong' group includes drugs that are pure agonists, whereas intermediate group includes partial agonists.

Table 2. *Classification of opioids*

Traditional	Origin	Function
Strong	**Naturally occurring**	**Pure agonists**
morphine	morphine	morphine
pethidine	codeine	fentanyl
fentanyl	papavarine	alfentanil
alfentanil	thebaine	remifentanil
remifentanil		sufentanil
sufentanil		
	Semisynthetic	**Partial agonist**
Intermediate	diamorphine	buprenorphine
buprenorphine	dihydrocodeine	
pentazocine	buprenorphine	**Agonists-antagonists**
butorphanol		pentazocine
nalbuphine		nalbuphine
		nalorphine
	Synthetic	
Weak	*Phenylpyperidines:*	
codeine	pethidine, fentanyl,	**Pure Antagonists**
	alfentanil, sufentanil	naloxone
	Diphenylpropylamines:	naltrexone
	methadone,	
	dextropropoxyphene	
	Morphinans:	
	butorphanol, levorphanol	
	Benzomorphans:	
	pentazocine	

PHARMACOLOGICAL ACTIONS OF OPIOID AGONISTS

Central nervous system
Analgesia
• Most effective in relieving dull, continuous and poorly localised pain arising from deeper structures, for example the gut. Less effective against superficial and sharp pain.

• Neuropathic pain can be very resistant, but patients may report that pain is still present, but the intensity is decreased and it no longer bothers them as much.

Sedation
• Drowsiness, feeling of heaviness and difficulty in concentrating are common.

• Sleep may occur with relief of pain, although they are not true hypnotics.

Euphoria and dysphoria
• Morphine and other opioids cause a sense of contentment and well being (euphoria). If there is no pain, morphine may cause restlessness and agitation (dysphoria).

Hallucinations
• These are more common with KOP agonists, but morphine and other MOP agonists may also cause hallucinations.

Tolerance and dependence
• Tolerance is the decrease in effect seen despite maintaining a given concentration of a drug. The mechanism is not fully understood but could involve down regulation of opioid receptors or decreased production of endogenous opioids.

• Dependence exists when the sudden withdrawn of an opioid, after repeated use over a prolonged period, results in various physical and

psychological signs. These include; restlessness, irritability, increased salivation, lacrimation and sweating, muscle cramps, vomiting and diarrhoea.

Cardiovascular system

Mild bradycardia
- Common as a result of decreased sympathetic drive and a direct effect on the sino-atrial (SA) node.

Peripheral vasodilatation
- Caused by histamine release and reduced sympathetic drive may result in a slight fall in blood pressure that may be significant in hypovolaemic patients.

Respiratory system

Respiratory depression

- Mediated via MOP receptors at the respiratory centres in the brainstem.

- Respiratory rate falls more than the tidal volume and the sensitivity of the brain stem to carbon dioxide is reduced. Its response to hypoxia is less affected but if hypoxic stimulus is removed by supplemental oxygen then respiratory depression may be augmented.

- Concurrent use of other CNS depressants, for example benzodiazepines or halogenated anaesthetic, may cause marked respiratory depression.

Cough suppression
- Codeine suppresses coughing to a degree similar to morphine, but has lesser analgesic activity.

- Morphine and diamorphine are used in paroxysmal nocturnal dyspnoea, as they produce sedation, reduce preload and depress abnormal respiratory drive.

Gastrointestinal System
- Stimulation of the chemoreceptor trigger zone causes nausea and vomiting.

- Smooth muscle tone is increased but motility is decreased resulting in delayed absorption, increased pressure in the biliary system (spasm of sphincter of Oddi) and constipation.

Endocrine System
- The release of ACTH, prolactin and gonadotrophic hormone is inhibited. Secretion of ADH is increased.

Ocular effects
- MOP and KOP receptors in Edinger-Westphal nucleus of occulomotor nerve are stimulated by opioids resulting in constriction of the pupils (meiosis).

Histamine release and itching
- Some opioids cause histamine release from mast cells resulting in urticaria, itching, bronchospasm and hypotension.

- Itching occurs most often after intrathecal opioids and is more pronounced on the face, nose and torso.

- The mechanism is centrally mediated and may be reversed by naloxone.

Muscle rigidity
- Large doses of opioids may occasionally produce generalized muscle rigidity especially of thoracic wall and interfere with ventilation.

Immunity
- The immune system is depressed after long-term opioid abuse.

Effects on pregnancy and neonates
- All opioids cross the placenta and if given during labour, can cause neonatal respiratory depression.

- Chronic use by the mother may cause physical dependence in utero and lead to a withdrawal reaction in the neonate at birth that can be life threatening.

- There are no known teratogenic effects.

PHARMACOKINETICS OF OPIOID AGONISTS
There is substantial variability (3-5 fold) in the clinical response

Table 3. *Pharmacokinetics of commonly used opioids*

	Morphine	Pethidine	Fentanyl	Alfentanil	Remifentanil
pKa	8.0	8.5	8.4	6.5	7.1
Unionised at pH 7.4 (%)	23	5	9	90	68
Plasma protein bound (%)	30	40	84	90	70
Terminal half life (hrs)	3	4	3.5	1.6	0.06
Clearance (ml.min^{-1}.kg^{-1})	15-30	8-18	0.8-1.0	4-9	30-40
Volume of distribution (l.kg^{-1})	3-5	3-5	3-5	0.4-1.0	0.2-0.3
Relative lipid solubility	1	28	580	90	50

to opioids due to their pharmacokinetics and pharmacodynamics. Pharmacokinetic properties of the opioids commonly used in anaesthesia are displayed in Table 3.

Opioids are weak bases (pKa 6.5-8.7). In solution, they dissociate into ionized and unionized fractions, the relative proportions depend upon the pH of the solvent and their pKa. The unionized fraction is more diffusible than ionized form. In the acidic environment of stomach, opioids are highly ionized and therefore poorly absorbed. Conversely, in the alkaline small intestine, they are predominantly unionized and are readily absorbed. However, many opioids then undergo extensive first-pass metabolism in the intestinal wall and liver, resulting in low oral bioavailability. High lipid solubility facilitates opioid transport into the biophase or site of action. Consequently, high lipid solubility confers a more rapid onset of action.

Drugs with high lipid solubility, high unionized fraction or low protein binding in the plasma, demonstrate large volumes of distribution. Most opioids are extensively distributed in the body and their volumes of distribution exceed total body water. Small intravenous doses of short-acting opioids (like alfentanil, sufentanil or fentanyl) produce a short duration of action because plasma (and brain) concentrations remain above the threshold for therapeutic action for only a brief period as the drug rapidly redistributes from the CNS to other tissues. Larger doses produce longer durations of action because plasma concentrations remain above the threshold at the completion of drug redistribution and depend upon the slower elimination process to be reduced below the threshold level.

Opioids are metabolized mainly in the liver to both active and inactive compounds that are excreted in urine and bile. Morphine and other opioids are excreted partly in the bile as water-soluble glucuronides. In the gut, these glucuronides are metabolized by the normal gut flora to the parent opioid compound and reabsorbed (entero-hepatic recirculation). Highly lipid soluble opioids, for example fentanyl, may diffuse from the circulation into the stomach mucosa and lumen, where they are ionized and concentrated because of the low pH. Later, gastric emptying and reabsorption from the small intestine may produce secondary peak effect (gastro-enteric recirculation). Extra-hepatic metabolism is important for some opioids; the kidneys play a vital role in conjugating morphine, whereas blood and tissue esterases are responsible for remifentanil metabolism.

Opioids differ substantially in their durations of action. Explanations for these differences are complex and not always evident from their clearance and terminal half-lives. For example, an analgesic dose of morphine lasts longer than a dose of fentanyl producing an equivalent degree of analgesia; yet the half-life for morphine is shorter than fentanyl. In the case of morphine, its relatively long duration of action is a reflection of its relatively low lipid solubility and slow diffusion out of CNS tissue. Once it enters blood it is effectively cleared from plasma.

INDIVIDUAL OPIOIDS

Morphine
Morphine is a naturally occurring phenanthrene derivative. It is the standard drug against which all other opioids are compared.

Dose
- Morphine can be given orally, intramuscularly (IM), intravenously (IV), subcutaneously (SC), rectally, epidurally and intrathecally.

- The intramuscular dose is 0.1-0.2mg.kg^{-1}, time to peak effect is 30-60 minutes and duration of action is 3-4 hours. Intravenous administration should be titrated to effect (usually 1-2mg boluses), but the total dose is similar. The onset of action is slightly more rapid with following IV administration, as the main factor responsible for its latency is low lipid solubility and slow penetration of blood brain barrier. Morphine may be given epidurally at 10% and intrathecally at 1% of the parenteral dose.

Pharmacokinetics
- Morphine is extensively metabolized by the gut wall and the liver to morphine-3-glucuronide (M3G) (70%), morphine-6 glucuronide (M6G) (10%) and to sulphate conjugates. M6G is 10-20 times more potent than morphine and is normally excreted in urine.

- It accumulates in renal failure and accounts for increased sensitivity to morphine.

- Neonates are more sensitive than adults to morphine due to reduced hepatic conjugating capacity.

- In the elderly, owing to reduced volume of distribution, peak plasma level of morphine is higher compared to younger patient.

Effects
- The main effects are mediated through MOP receptors. It is a potent analgesic with good sedative and anxiolytic properties. It may cause euphoria, dysphoria and hallucination. It produces respiratory depression and cough suppression.

- It has minimal effect on cardiovascular system and may produce bradycardia and hypotension. Nausea and vomiting are common side-effects. Histamine release may lead to rash, itching and bronchospasm (in susceptible patients). Meiosis is common. Tolerance and dependence may develop.

Papaveretum
Papaveretum is a preparation containing a mixture of hydrochloride salts of opium alkaloids: morphine hydrochloride, codeine hydrochloride and papaverine hydrochloride. Prior to 1993, the preparation also contained noscapine, however this was removed after it had been shown to be teratogenic in animal studies.

Dose
- It can be given subcutaneously, intramuscularly or intravenously. 15.4mg of papaveretum contains 10mg of morphine.

- It is used for moderate to severe pain and preoperative sedation.

Effects
- In comparison with morphine, it provides greater degree of sedation for a given level of analgesia with fewer gastrointestinal side-effects.

- Higher doses of papaveretum are associated with transient but severe headache. This effect, linked most likely to its papaverine content, reduces the compound's addiction potential.

- Most anaesthetists feel that the added expense of the mixture is not justified because in the concentration used, morphine is the only active ingredient.

Codeine

Codeine is a natural opioid and one of the principal alkaloids of opium. It has very low affinity for opioid receptors.

Dose
- Can be given orally and IM. The dose for an adult is 30-60mg by either route and can be repeated at 6 hour intervals, if required. Varying doses of codeine (8-30mg) are commonly incorporated with NSAIDs in compounds employed in the treatment of mild to moderate pain.

- Codeine is also used in antitussive and antidiarrhoeal preparations.

Pharmacokinetics
- Oral bioavailability of codeine is 50%. About 10% is metabolized to morphine and the rest is metabolized to inactive conjugated compounds.

- Metabolism to morphine depends on an isoform of cytochrome p450, which exhibits polymorphism, thus poor metabolizers (approximately 10% people) may experience minimal pain relief.

Effects
- It causes little euphoria and has low abuse potential. Codeine is less sedative and less likely to cause respiratory depression than morphine. It may cause disorientation and excitement.

- Constipation is common side effect.

- Dihydrocodeine is a semi-synthetic derivative of codeine with similar pharmacologic effects.

- Oxycodone is more effective, but has higher abuse potential.

Diamorphine (heroin)

A semi-synthetic opioid, the diacetylated analogue of morphine. It is 1.5-2.0 times more potent than morphine. It is a pro-drug and is converted to the active components of acetylmorphine and morphine by esterases in the liver, plasma and central nervous system.

Dose
- Diamorphine can also be given by the same routes as morphine in approximately half the dose. Due to its higher lipid solubility, it is less likely than morphine to cause delayed respiratory depression when used epidurally or intrathecally.

- It can be administered as hydrochloride salt by IM or SC infusion in a smaller volume of solution than an equivalent dose of morphine. This is an important consideration for patients with terminal malignant disease who may require large doses of opioid for pain relief.

Pharmacokinetics
- Diamorphine is 200 times more lipid soluble than morphine and, therefore, passes more rapidly across the blood-brain barrier into the CNS where it is converted to morphine. Therefore, it has more analgesic potency and a more rapid onset of action than morphine.

- Because of the extensive first pass metabolism, it has low bio-availability.

Effects
- It shares common opioid effects with morphine. It is associated with an increased tendency to cause euphoria and dependency.

- May cause less nausea and vomiting than morphine.

Pethidine (mepiridine)

It is a synthetic phenylpyperidine derivative and was originally developed as an antimuscarinic agent.

Dose
- Pethidine is available as 50mg tablets and ampoules of different strength (10mg.ml^{-1} and 50mg.ml^{-1}).

- For acute pain, it can be administered orally (50-150mg), SC (50-100mg), IM (50-100mg) or IV (25-100mg). The doses can be repeated every 4 hours.

Pharmacokinetics
- Pethidine is 30 times more lipid soluble than morphine. Oral bioavailability is 50%.

- It is metabolized in the liver by ester hydrolysis to norpethidine and pethidinic acid that are excreted in the urine and therefore accumulate in renal failure. At higher concentration, norpethidine can produce hallucination and convulsions.

- Pethidinic acid is an inactive compound.

- Pethidine is often used for labour analgesia. It readily crosses the placenta, and a significant amount reaches to the foetus over several hours.

Effects
- There are some pharmacological differences from morphine. It produces tachycardia, dry mouth and less marked meiosis. However as is the case with morphine, a significant decrease in BP may occur when pethidine is administered to elderly or hypovolaemic patients.

- It may produce less biliary tract spasm than morphine. Pethidine is absolutely contraindicated in patients on monoamine oxidase inhibitors (MAOI), as serious side effects like hypotension or hypertension, hyperpyrexia, convulsion and coma may occur.

- The underlying mechanism is not clear but may involve reduced metabolism of pethidine by MAOI and pethidine's effect on turnover of 5- hydroxytryptamine in the brain.

Fentanyl

It is a synthetic phenylpyperidine derivative and is 100 times more potent than morphine.

Dose
- Fentanyl is available as a colourless solution for injection in 2 and 10ml ampoules containing 50mcg per ml.

- When given in small doses (1-2mcg.kg^{-1}), it has rapid onset and a short duration of action (30 minutes). Such doses are used intravenously for pain associated with minor surgery. In small doses it has little sedative effect.

- Higher doses are used to obtund sympathetic response to laryngoscopy and intubation.

- Fentanyl has been used to augment effects of local anaesthetics in spinal and epidural analgesia at 10-25mcg and 25-100mcg doses respectively.

- Fentanyl is also available as a transdermal patch for chronic pain conditions and as a lollipop to premedicate children.

Pharmacokinetics
- Fentanyl is 500 times more lipid soluble than morphine, consequently it is rapidly and extensively distributed in the body (volume of distribution 4l.kg^{-1}). At small doses (1-2mcg.kg^{-1}), plasma and CNS concentrations may decrease quickly to below an effective level during the rapid distribution phase.

- However, following prolonged administration or with high doses, its duration of action is significantly prolonged. In these circumstances, the distribution phase is complete while the plasma concentration is still high. Recovery from the effect of the drug then depends on its slow elimination from the body (terminal half life 3.5 hours).

- Fentanyl is predominantly metabolized in the liver to norfentanyl which is inactive. The metabolite is excreted in the urine over a few days.

Effects
- Many properties of fentanyl are similar to morphine. It produces respiratory depression in a dose-dependent manner.

- Large doses (50- 100 microgram/kg) have been used for cardiac surgery to obtund metabolic stress response. At such high doses, sedation is profound and unconsciousness may occur. In addition, muscular rigidity of the chest wall may affect ventilation.

Alfentanil
Alfentanil is a synthetic phenylpiperidine derivative structurally related to fentanyl; it has 10-20% of its potency.

Dose
- Alfentanil is available as colourless solution in the concentrations of 500mcg.ml^{-1} or 5mg.ml^{-1}. It may be administered intravenously as either a bolus or continuous infusion.

- Bolus doses (10mcg.kg^{-1}) are useful for short term analgesia and attenuation of the cardiovascular response to intubation. Continuous infusions (0.5-2.0mcg.kg^{-1}.min^{-1}) are used in the intensive care unit for sedation in patients on mechanical ventilation.

Pharmacokinetics
- Although it has much lower lipid solubility than fentanyl, the lower pKa of alfentanil (6.5 versus 8.4 for fentanyl) means that more alfentanil is present in the unionized form compared to fentanyl (89% compared to 9%). Consequently, its onset of action is more rapid.

- Because of its lower lipid solubility, less alfentanil is distributed to muscles and fat. Hence, its volume of distribution is relatively small and more of the dose remains in blood from which it can be cleared by the liver.

- Even though alfentanil has a lower clearance rate, this is more than offset by its reduced volume of distribution and its half life is relatively short.

Effects
- Most effects of alfentanil are similar to fentanyl but with quicker onset and shorter duration of action.

Remifentanil
It is a synthetic phenylpiperidine derivative of fentanyl with similar potency but is ultra short-acting.

Dose
- It is available as white crystalline powder in glass vial containing 1, 2 or 5mg remifentanil hydrochloride.

- A range of infusion rates (0.05-3.0mcg.kg^{-1}.min^{-1}) are used during maintenance of anaesthesia with controlled ventilation.

Pharmacokinetics
- Remifentanil is rapidly broken down by non-specific plasma and tissue esterases resulting in a short elimination half life (3-10 minutes).

- It is context insensitive, in that the half life, clearance and distribution are independent of duration and strength of infusion.

Effects
- Certain properties of remifentanil like rapid onset, rapid offset, organ independent metabolism and lack of accumulation make it suitable for use during various surgical procedures. However, it should be used cautiously at higher rates of infusion as serious side effects for example bradycardia, hypotension, apnoea and muscle rigidity may occur.

- Since there is no residual effect, alternative postoperative analgesic regimen should be established before infusion is terminated.

Tramadol
Tramadol is phenylpiperidine analogue of codeine. It is weak agonist at all opioid receptors with 20-fold preference for MOP receptors. It inhibits neuronal reuptake of norepinephrine. It potentiates release of serotonin and causes descending inhibition of nociception.

Dose
- Oral and parenteral dosage requirements are similar, 50-100mg 4 hourly.

Pharmacokinetics
- Tramadol has high oral bioavailability of 70% which can increase

to 100% with repeated doses due to reduction in first pass effect. It is 20% bound to plasma proteins.

- It is metabolized in the liver by demethylation into a number of metabolites - only one of them (O-desmethyltramadol) has analgesic activity. Its volume of distribution is 4l.kg^{-1} and its elimination half-life is 4-6 hours.

Effects
- In equi-analgesic dose to morphine, tramadol produces less respiratory and cardiovascular depression than morphine.

- Constipation is less common, however tramadol shares most of the common side effects of other opioids (e.g. vomiting, drowsiness and ambulatory dizziness).

- Tramadol is contra-indicated in patients on MAOI or with a history of epilepsy.

Methadone
A potent opioid analgesic that is well absorbed with good oral bioavailability (75%). However, its main use is as a substitute for opioids, for example diamorphine (heroin) in addicts because its slow onset and offset reduces the incidence of withdrawal symptoms. It is itself addictive.

PARTIAL OPIOID AGONISTS
These drugs have affinity for opioid receptors but low intrinsic activity compared to full agonists. Because of their reduced activity, they are able to antagonise or reduce the responsiveness of a pure agonist like morphine when acting at the same receptor. In other words, a higher dose of a pure agonist is required in presence of partial agonist, in order to obtain full agonist response. They can be further divided into two groups:

1. **Mixed agonist-antagonist**. They exert agonist effects at one opioid receptor and antagonistic effects at the other. Examples are pentazocine, nalbuphine and meptazinol.

2. Drugs that do not display antagonistic effects but have diminished effects at opioid receptors.

Meptazinol
Meptazinol is a synthetic analgesic with mixed agonist-antagonist activity at opioid receptors. It also has an action via central cholinergic pathways that may contribute to analgesia. It produces less respiratory depression because of its selectivity for MOP-1 receptors. Its main disadvantage is a high incidence of nausea and vomiting, that can be reduced by administration of antimuscarinic drugs. It is one-tenth as potent as morphine. It has rapid onset of action that lasts for 2-4 hours.

Buprenorphine
Buprenorphine is 30 times more potent than morphine. It is highly lipid soluble, and is well absorbed sublingually. It has low oral bioavailability. Although its terminal half-life is 3-4 hours, it has a much longer duration of action (up to 8 hours). In general,

buprenorphine and morphine produce similar effects and side effects. As buprenorphine has extremely high affinity for MOP receptors, its effects are not completely reversed by naloxone (see opioid antagonists). Respiratory depression may need to be treated with doxapram. Nausea and vomiting are severe and prolonged.

Pentazocine
Pentazocine has 25% of the analgesic potency of morphine. It is not very effective in relieving severe pain, and this may be partly because of absence of euphoriant effect. It produces an increase in heart rate and blood pressure. Nausea, vomiting, bizarre dreams and hallucinations are more common than morphine.

OPIOID ANTAGONISTS
Naloxone and its longer acting derivative naltrexone occupy opioid receptors, but they have essentially no intrinsic activity at these receptors. Moderate doses administered in the absence of an opioid produce no effect; large doses, however, may have effects in which antagonism of endorphins may play a role.

Naloxone
Naloxone is a pure opioid agonist and will reverse opioid effects at MOP, KOP and DOP receptors, although its affinity is highest at MOP receptors.

It is the drug of choice for the treatment of opioid induced respiratory depression. The usual dose is 200-400mcg intravenously, titrated to effect. It is imperative the naloxone be administered slowly to avoid reactive pulmonary hypertension with the development of acute pulmonary oedema probably from antagonism of endogenous opioid effects. Smaller doses (0.5-1.0mcg.kg^{-1}) may be titrated to reverse undesirable effects of opioids, for example itching associated with the intrathecal or epidural administration of opioids, without significantly affecting the level of analgesia. The duration of effective antagonism is limited to around 30 minutes and therefore longer acting agonists will outlast this effect and further bolus doses or an infusion (5-10mcg.kg^{-1}.h^{-1}) will be required to maintain reversal. Caution must be used in opioid addicts as giving naloxone may cause an acute withdrawal state with hypertension, pulmonary oedema and cardiac arrhythmias. Antanalgesic effects may be observed in opioid naïve subjects who are given naloxone.

Naltrexone
Naltrexone has similar mechanism of action, but has few pharmacokinetic advantages compared to naloxone. It has a longer half-life and is effective orally for up to 24 hours. It has been used to treat opioid addiction and compulsive eating with morbid obesity.

FURTHER READING
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